New Methods for

Palladium-catalyzed Decarboxylative Benzylation, Arylation and Dearomatization Reactions

By

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Submitted to the graduate degree program in Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Date Defended: August 13th, 2015

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New Methods for
Palladium-catalyzed Decarboxylative Benzylation, Arylation and Dearomatization Reactions

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Abstract

Development of novel synthetic methods for the efficient generation of new carbon-carbon bonds is a valuable endeavor in organic synthesis. In this regard, palladium-catalyzed decarboxylative cross-coupling has significant potential as a waste-free reaction manifold with increased functional group tolerance due to the avoidance of preformed organometallics and basic reagents. Since the initial reports by Saegusa and Tsuji on decarboxylative allylation (DcA) of β-ketoesters in 1980, this concept remained relatively unexplored until the independent reports from Tunge and Stoltz in 2004. Since then, couplings of a broad array of nucleophiles, as well as asymmetric variants of the DcA reactions, have been heavily developed. However, due to the inherently low reactivity of benzyl electrophiles, catalytic decarboxylative benzylation reactions are comparatively less developed.

Presented herein are the developments of new methods for the catalytic decarboxylative benzylic cross-coupling reactions with weakly-stabilized nucleophiles. In particular, the benzyl alkyne cross-coupling, which was initially limited to extended aryl systems, was further developed to allow couplings of primary benzyl electrophiles without extended π-conjugation. Our efforts were then directed toward developing a highly stereospecific decarboxylative coupling of acetylides and ketone enolates with secondary benzyl electrophiles that possess a 1,1-diarylmethane structure. The coupling of secondary benzyl electrophiles with acetylides proceeded with high stereospecificity to provide enantioenriched 1,1-diarylethynyl methanes, and we are unaware of any other method for the direct synthesis of such motifs. However, racemization was observed in the decarboxylative coupling of enantioenriched benzylic β-ketoesters.

In the search for a new method to couple secondary benzyl electrophiles with ketone enolates, we serendipitously discovered the unprecedented catalytic decarboxylative dearomatization and

arylation reactions of ketone enolates. Two sets of protocols involving simple variation of ligands were then developed for the selective decarboxylative dearomatization or arylation of enolates. These methods provided alicyclic and mono-α-arylated ketones in a highly regioselective manner and the expected benzylation of ketone enolates was never observed. Additionally, initial results have also shown that the palladium-catalyzed decarboxylative dearomatization of benzyl carbonates is highly stereospecific.

To my love, Gayan

and

to my loving parents, Nayana and Boniface

Acknowledgements

I am deeply indebted to my research advisor and mentor, Dr. Jon Tunge. Jon, you have been an excellent teacher and a great mentor to me throughout the last five years. I feel really privileged to complete my graduate career at KU under your mentorship, and I cannot thank you enough for making me a part of your research group. I have absolutely loved being in lab since I entered it on day one, and I greatly enjoyed doing research. I am really grateful to you for making me the chemist and researcher who I am today. Your advice and suggestions have continuously provided me with the strength and courage I needed to achieve my goals. While moving on is bittersweet, I wish you and the group the very best.

To Dr. Paul Hanson, thank you for being an excellent teacher. I absolutely loved your synthesis class. The energy and liveliness you bring to class room teaching, problem sets and MOS is invaluable. I should also mention that I could never forget your encouraging feedback after my research presentation. To Dr. Helena Malinakova, thank you for your support during my long talk preparation as well as in the Organic Synthesis II class. I would also like to thank Dr. Ryan Altman and Dr. Misha Barybin for serving on my oral exam committee and dissertation committee. Special thanks go out to Dr. Victor W. Day for solving the x-ray crystal structure and Dr. Justin Douglas for support with NMR characterization. Dr. Daryle Busch, thank you for replying to my numerous e-mails and providing me with valuable advice before I joined KU.

I had the privilege of working with some of the finest colleagues I could ask for. Past members in the Tunge group, Alex, Tony, Yamuna and Ram thank you all for your support. Robert, thanks for helping me initially to get started in the lab. Thanks to all the present Tunge group members for creating a cheerful working environment. Tapan, thank you for your friendship, and all of the help along the way. I really value the discussions we had and your feedback for talks, manuscripts as well as in thesis writing. James, thanks for everything, especially for your help when I was

preparing for my orals. Mary, thank you for the edits throughout my dissertation. They were greatly useful. Thanks for your unfailing willingness to help beyond chemistry. Theresa and Simon, thanks for the edits in chapters in the dissertation and for your help in fixing issues in the lab. Kevin and Richard, I'm sure you will do great in the Tunge lab. You guys all made my stay at KU a pleasant and memorable one. Jordie, I really enjoyed working with you over the summer, and I wish you all the very best in succeeding in your future goals.

The professors at University of Colombo, Sri Lanka also deserve appreciation. I am thankful to all my professors in the Department of Chemistry at UOC, and especially to my undergraduate research advisor Dr. Rohini M. de Silva, for her advice and support in applying for graduate studies. I would certainly not be here at KU without their support.

None of this would have been possible without the love and support of my family. First, to my loving parents, ammi and thaththi, I'm very thankful to you for giving me the best education, and bringing me up with so much love and protection. Ammi, you are my first science teacher, and I want to thank you for always believing in me. Thaththi, I know you have very high expectations of us, and today I know you are one proud dad. My loving sisters Hiranya and Laksheen, thank you for your love and support. Hiranya, I never thought we'd end up together on the 6th floor of Malott Hall at KU, and I'm sure I'm going to miss you. Laksheen, thank you for your calls from miles away. I'd also like to thank my wonderful in-laws for their love throughout the years.

Beyond everything my heartfelt thanks goes to my loving husband Gayan, your unconditional love, support and understanding has always helped me to maintain a balanced life between research and outside the lab. I feel so lucky to be your wife and I'm eagerly waiting to start the next chapter of our lives with the blessed assurance of the Almighty Father. Finally, and most importantly I thank God for blessing me with good health, and for giving me the strength to accomplish my goals.

Table of Contents

Abbreviations

Ac	acetyl
acac	acetylacetone
Ar	aryl
BEt_3	triethylborane
BF_4	tetrafluoroborate
Bn	benzyl
BSA	*N*,O-bis(trimethylsilyl)acetamide
Bu_3Sn	tributyltin
Cbz	Benzyloxycarbonyl
cee	conservation of enantiomeric excess
CF_3	trifluoromethyl
CO	carbon monoxide
CO_2	carbon dioxide
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cs_2CO_3	cesium carbonate
Cy	cyclohexyl
dba	dibenzylideneacetone
dmdba	dimethoxydibenzylideneacetone
DcA	decarboxylative allylation
DcB	decarboxylative benzylation
DCC	*N*,*N*-dicyclohexylcarbodiimide

DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
GC	gas chromatography
Het	heteroaromatic
HPLC	high performance liquid chromatography
K_2CO_3	potassium carbonate
$KN(SiMe_3)_2$	Potassium hexamethyldisilazide
L_n	ligand
LAH	lithium aluminum hydride
LG	leaving group
Me	methyl
MeCN	acetonitrile

NaH	sodium hydride
n-BuLi	n-butyllithium
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
NR	no reaction
Nu	nucleophile
OMe	methoxy
PBu_3	tributylphosphine
Pd	palladium
PPh_3	triphenylphosphine
Ph	phenyl
Pr	propyl
rac-BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
SIMes	*N*,*N*'-bis[2,4,6,-(trimethyl)phenyl]imidazolidin-2-ylidine)
S_N2	bimolecular nucleophilic substitution
t-Bu	*tert*-butyl
t-BuOK	potassium *tert*-butoxide
THF	tetrahydrofuran
Tol	toluene

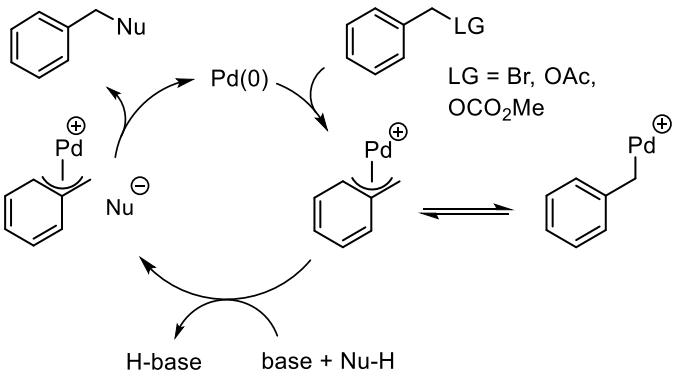
Chapter 1

Palladium-catalyzed Benzylic Functionalization

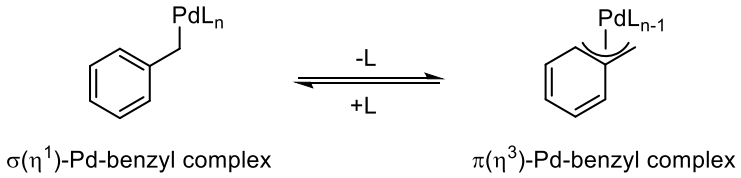
1.1 Introduction

Activations and functionalizations of benzylic derivatives by palladium-catalysts have paved the way to the development of new reactions in organic synthesis. The versatility, efficiency, and relatively mild conditions required in palladium-catalyzed cross-coupling reactions have made them very attractive compared to classical benzylic functionalization reactions. While there are reports of using various late transition metals in catalytic benzylic cross-coupling reactions, nickel and palladium are more widely used.[1] Initial reports of palladium-catalyzed benzylic cross-couplings were mainly limited to the oxidative addition of benzyl halides or pseudohalides to Pd(0) to generate electrophilic palladium-benzyl complexes. Much later, it was discovered that benzyl acetates and carbonates also undergo oxidative addition with Pd(0), generating the electrophilic palladium-benzyl complexes, similar to analogous allyl substrates.[2] Examples of nucleophilic coupling partners of benzylic cross-coupling reactions include, but are not limited to, active methylene compounds,[3] heteroatomic nucleophiles (phenols, amines, sulfones),[3d, 4] olefins,[5] preformed organometallics,[6] aromatics,[7] and heteroaromatics.[8]

A generalized catalytic cycle for the palladium-catalyzed benzylic cross-coupling is depicted in Scheme 1.1. Benzyl halides, acetates, or carbonates undergo oxidative addition to Pd(0), generating the Pd-benzyl complex, which can isomerize between the $\sigma(\eta^1)$ and $\pi(\eta^3)$ benzyl complexes. The formation of the η^3-Pd-benzyl complex results in partial loss of aromaticity (Scheme 1.2). Subsequent nucleophilic attack on the palladium-benzyl complex results in the formation of the benzylated product (Scheme 1.1).



Scheme 1.1



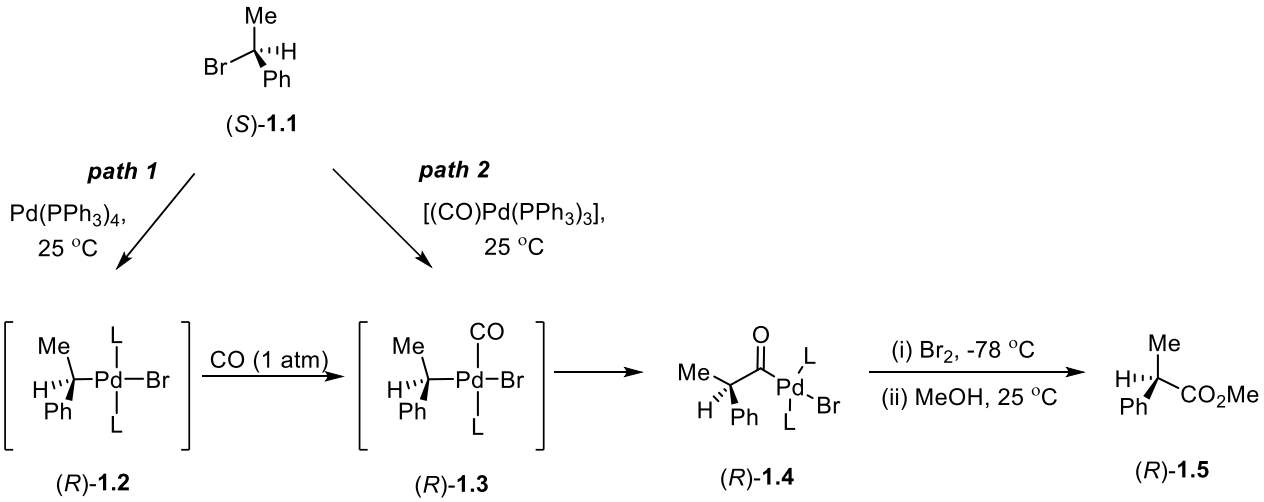
Scheme 1.2

1.2 Reactivity and isolation of η^3-palladium-benzyl complexes

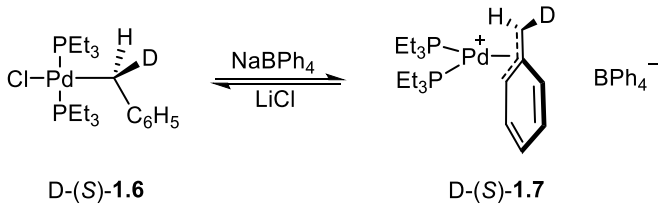
Stereochemical studies on oxidative addition of benzyl halides to zero-valent palladium complexes was reported by Stille (Scheme 1.3).[9] In the presence of $Pd(PPh_3)_4$ and $[(CO)Pd(PPh_3)_3]$, oxidative addition of benzyl halides to Pd(0) is followed by CO insertion (path 1 and path 2 respectively). The insertion of carbon monoxide is thought to occur more rapidly than β-hydride elimination. The enantioenriched (*S*)-α-phenylethyl bromide **1.1** delivered (*R*)-**1.4** in both reaction pathways. From this data, the stereospecificity for the oxidative addition step, **1.1** to **1.2** was determined to be 95%. The product (*R*)-**1.4** was converted to (*R*)-**1.5** to determine the absolute configuration. The observed inversion of configuration in (*R*)-**1.4** results from the oxidative addition step, as the carbonyl insertion occurs with retention. Therefore, these experiments led to the conclusion that the oxidative addition of benzyl halides to Pd(0) occurs via

an S_N2 displacement with inversion of configuration at the benzylic carbon. These results were further confirmed by the stereochemical studies conducted using optically enriched PhCHDCl.[9]

Studies on the mechanism of interconversion between η^1 and η^3 Pd-benzyl intermediates were also undertaken by Stille (Scheme 1.4).[10] When enantioenriched deuterated D-(*S*)-η^1 benzyl intermediate D-(*S*)-**1.6** is treated with $NaBPh_4$, the resulting D-(*S*)-η^3-palladium-π-benzyl intermediate D-(*S*)-**1.7** retains its optical activity at ambient temperature. Treatment of D-(*S*)-**1.7** with LiCl regenerates D-(*S*)-**1.6** with 94% net retention at the benzylic carbon. From these results it was evident that the π-σ-π interconversion of palladium-benzyl complexes occurs with high stereospecificity.

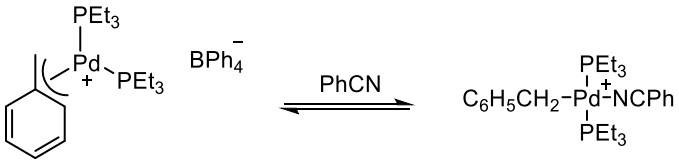


Scheme 1.3



Scheme 1.4

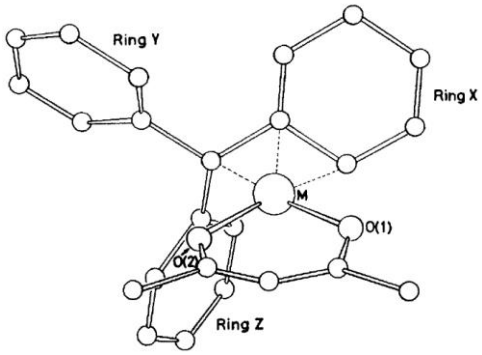
Temperature dependent NMR spectroscopic studies of non-deuterated racemic **1.7** in coordinating benzonitrile solvent support the presence of an equilibrium in solution between the η^3-Pd-π-benzyl (**1.7**) and η^1-Pd-benzyl (**1.8**) complexes (Scheme 1.5).[10] Such an isomerization is not observed in non-coordinating solvents. These results suggest that the η^3-palladium-π-benzyl intermediates are more favored in non-coordinating solvents, while η^1-palladium-σ-benzyl intermediates are favored only in coordinating solvents, where an exogenous ligand is present to stabilize the η^1 16-electron complex.

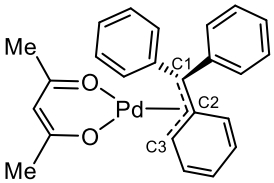


1.7 **1.8**

Scheme 1.5

The first x-ray crystal structure of a palladium-π-benzyl complex, [Pd(acac)η^3-triphenylmethyl] **1.9**, was reported in 1978 (Figure 1.1).[11] The x-ray crystallographic data of **1.9** clearly shows that the palladium is bound to the C1 and C3 carbons. The bond lengths of Pd–C1, Pd–C2, and Pd–C3 were determined to be 2.105, 2.154 and 2.200 Å respectively.



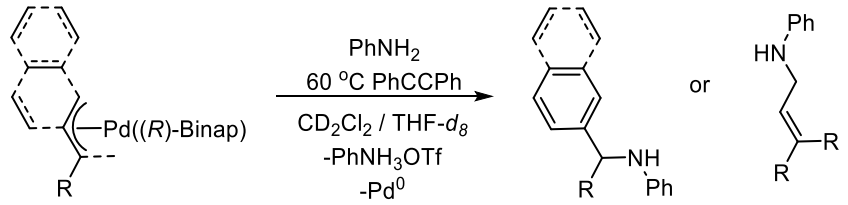


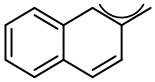
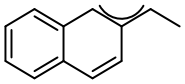
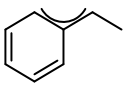
1.9

Figure 1.1 The X-ray crystal structure of [Pd(acac)η^3-triphenylmethyl]
Figure taken from ref [11]

Other reported η^3-metal-benzyl complexes (Fe, Co, Rh, Ni, and Pt) also show a similar trend where the Metal–C1 bond length is much shorter than Metal–C3 bond length.[2] This in turn suggests that the benzylic carbon C1 might be more electrophilic compared to the *ortho*-carbon C3. Additionally, the reported η^3-Pd-heteroaryl methyl complexes show similar characteristics.[12] Since Pd-π-benzyl complexes are electrophilic, they undergo nucleophilic addition reactions. The studies on relative rates for the amination of η^3-allyl and η^3-benzyl complexes show that the rate of amination of Pd-η^3-benzyl is much higher than that of Pd-η^3-allyl complexes (Table 1.1).[13] These observations were also supported by APT charge calculations, which show that the benzyl carbon has a higher electrophilicity compared to the allyl carbons.[13]

Table 1.1



η3 electrophile	$t_{1/2}$ (min) [a]	k_{obs} (s^{-1}) x 10^3 [a]
	11	1.0
	42 (15)	0.27 (0.79)
	185 (159)	0.062 (0.072)
	570 (7.1)	0.020 (1.63)
	2200 (250)	0.0052 (0.046)

Reaction conditions: 0.022 M Pd complex, 1.08 M aniline, 0.22 M PhCCPh, 9.0 M 1,3,5-trimethylbenzene (internal standard) in 0.2 mL of CD_2Cl_2 and 0.6 mL of THF-d_8 at 60 °C. [a] Results in parentheses were obtained from reactions in 0.8 mL of DMSO-d_6.

In most of the reactions, which involve η^3-palladium-π-benzyl intermediates, the rate limiting step is the formation of those intermediates. This high energy barrier is resulted due to the energetic cost of dearomatization. With aromatic systems having extended π-conjugation, e.g. naphthalene (**1.10**), the formation of η^3-Pd-[(naphthyl)methyl] complex has a lower energy barrier compared to the η^3-Pd-benzyl complex (**1.11**) due to the lower resonance energy per ring of naphthalene than that of benzene (~25 kcal/mol vs 36 kcal/mol respectively).[14] The relative ease of formation of Pd-π-benzyl/allyl intermediates is shown in Figure 1.2.

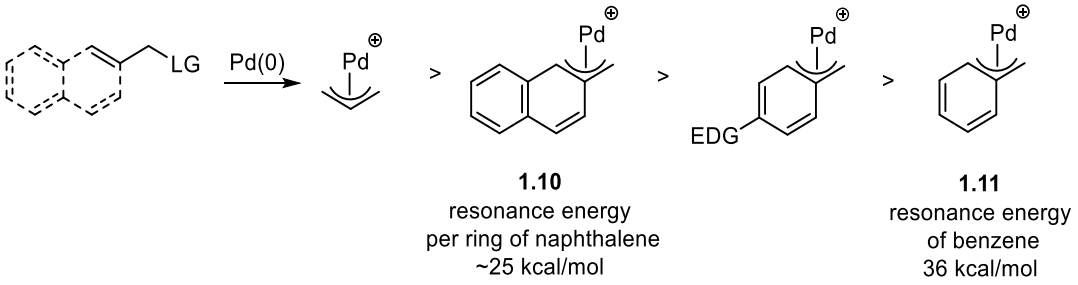
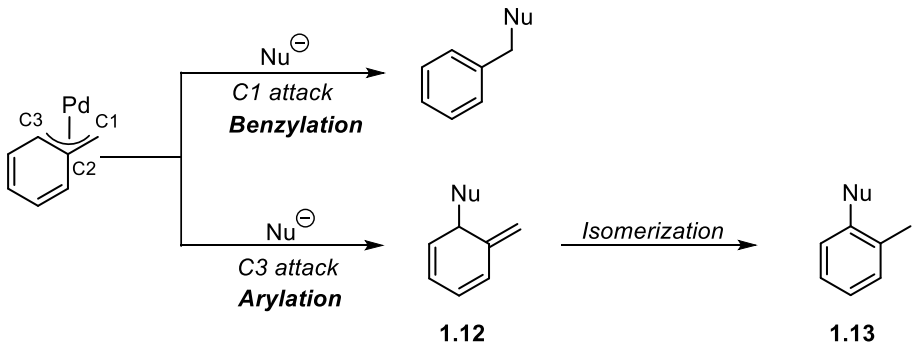


Figure 1.2

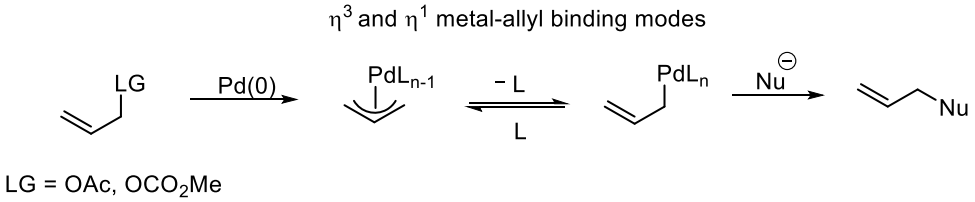
As stated earlier, benzylic carbon (C1) of the η^3-Pd-π benzyl intermediate is more electrophilic than its *ortho*-carbon (C3), as supported by Hartwig's APT charges for the benzyl system for C1, C2 and C3, which are 0.343, -0.193 and 0.122 respectively. In addition, nucleophilic addition to the benzylic position allows the Pd-π-benzyl or (naphthyl)methyl system to regain aromaticity, whereas nucleophilic addition to the *ortho*-carbon provides a dearomatized product (**1.12**) which can only aromatize by isomerization to the arylated product (**1.13**) (Scheme 1.6). Therefore, in most reactions, nucleophiles regioselectively attack the benzylic carbon. However, under the appropriate conditions, nucleophilic additions at the *ortho*-carbon have also been reported.[15] (This section will be covered in detail in Chapter 4).



Scheme 1.6

1.3 Palladium-catalyzed nucleophilic substitution reactions of benzylic carboxylates and benzylic carbonates

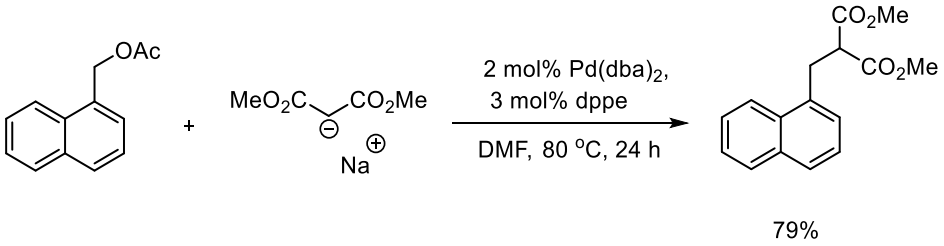
In addition to benzyl halides, benzyl acetates, carbonates, and phosphates also undergo palladium-catalyzed nucleophilic substitution at the benzylic carbon, similar to allyl derivatives used in the Tsuji-Trost allylic alkylation.[1b] In a typical Tsuji-Trost reaction, allyl acetates or carbonates undergo oxidative addition to Pd(0) to generate η^3-allyl palladium intermediates, which can undergo substitution by a nucleophile to provide the allylated product (Scheme 1.7).



Scheme 1.7

Similarly, benzyl acetates or carbonates can undergo oxidative addition to Pd(0), generating η^3-benzyl palladium intermediates. The nucleophilic substitution of naphthylmethyl acetates under palladium-catalyzed conditions was first reported by Fiaud in 1992 (Scheme 1.8).[3a] However, under identical conditions benzyl acetates failed to undergo benzylic substitution with sodium

dimethyl malonate (Scheme 1.9); later Kuwano reported the nucleophilic substitution of benzylic acetates by stabilized nucleophiles in the presence of dppf-[Pd(allyl)cod]BF_4.[16] In addition to malonate nucleophiles, palladium-catalyzed benzylic substitution by amines and amine equivalents (DMF) has also been reported.[16-17]



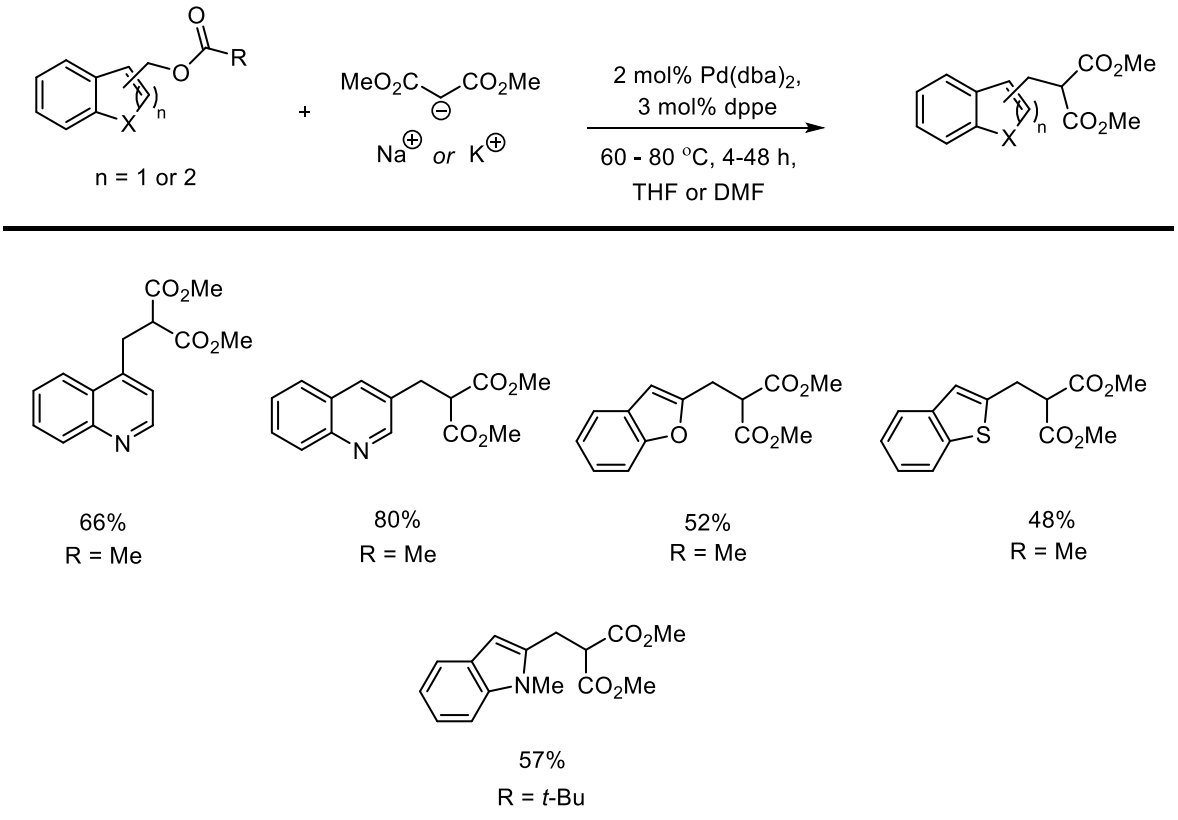
Scheme 1.8

Scheme 1.9

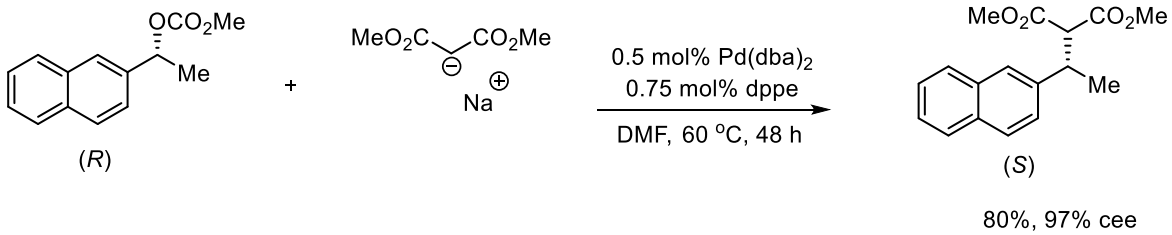
In a later report, Fiaud reported that heteroaromatic electrophiles (quinolines, benzofurans, benzothiophenes and indoles) with extended π-conjugation and a carboxylate leaving group also undergo palladium-catalyzed nucleophilic substitution with malonate nucleophiles (Scheme 1.10).[3c, 18]

Fiaud also showed that the palladium-catalyzed benzylic substitution of enantioenriched naphthylethyl carbonates with soft malonate nucleophiles is highly stereospecific, and occurs with overall retention of configuration.[3b] An optimal yield and stereospecificity was obtained with 0.5 mol% $Pd(dba)_2$ and the achiral bidentate ligand, dppe (Scheme 1.11). In these stereospecific

benzylic substitution reactions carbonates proved to be the superior leaving group compared to acetate and provided high enantiomeric excess in the final product. Complete retention of stereochemistry was also observed in stereospecific allylic substitution reactions with soft malonate nucleophiles, in which a double S_N2 displacement mechanism was proposed at the carbon undergoing substitution.[19] The inert nature of benzyl acetates and the overall retention observed with optically active naphthylethyl carbonates suggests a similar mechanism for palladium-catalyzed benzylic alkylation reactions and Tsuji-Trost allylic alkylations.

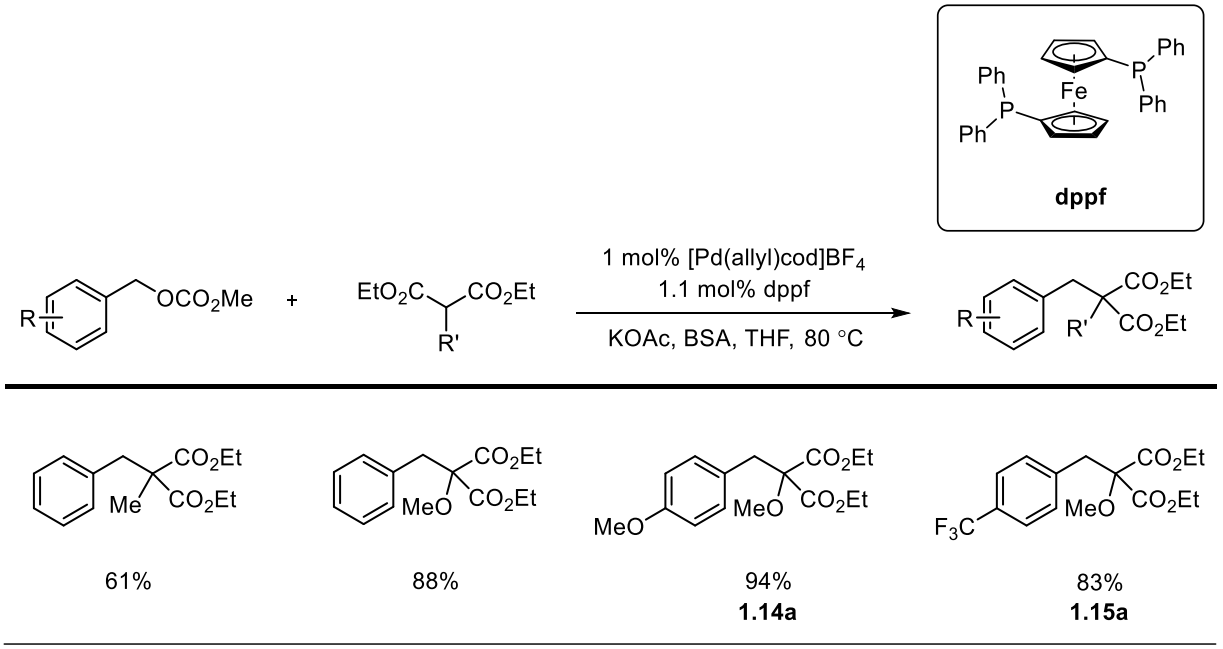


Scheme 1.10

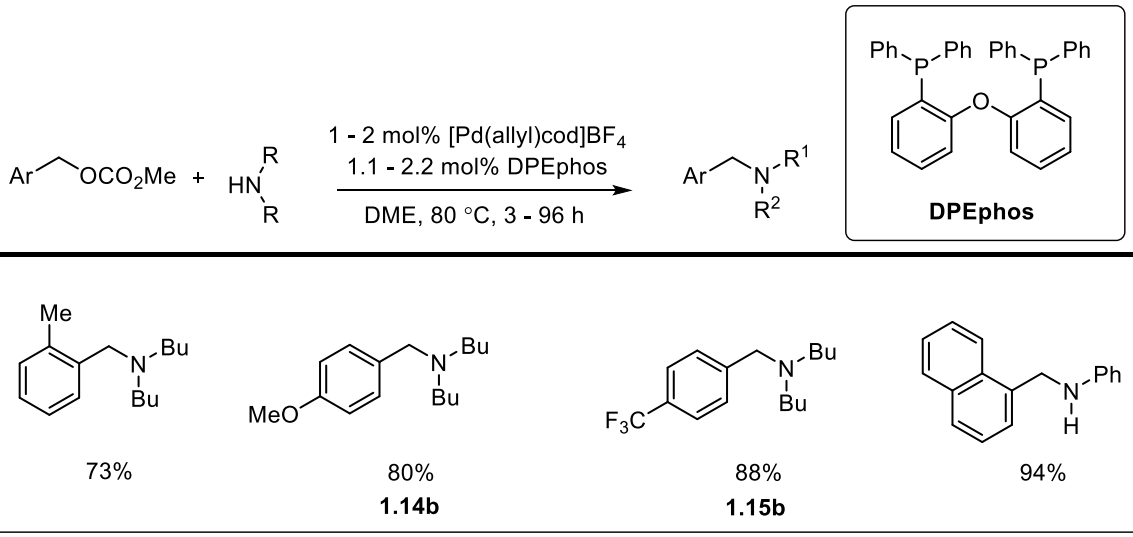


Scheme 1.11

In 2003, Kuwano and co-workers extended the electrophile scope of the palladium-catalyzed benzylic alkylation reactions to benzyl carbonates.[3d] In the presence of [Pd(allyl)cod]BF_4, dppf and a stoichiometric quantity of base (BSA), malonates (Scheme 1.12) and amine nucleophiles (Scheme 1.13) undergo alkylation to provide the benzylated products. Electron donating methoxy (OMe)-**1.14** as well as electron withdrawing trifluoromethyl (CF_3)-**1.15** substituents on the phenyl ring provided very good yields in benzylic substitution reactions with malonate as well as with amine nucleophiles.[3d]

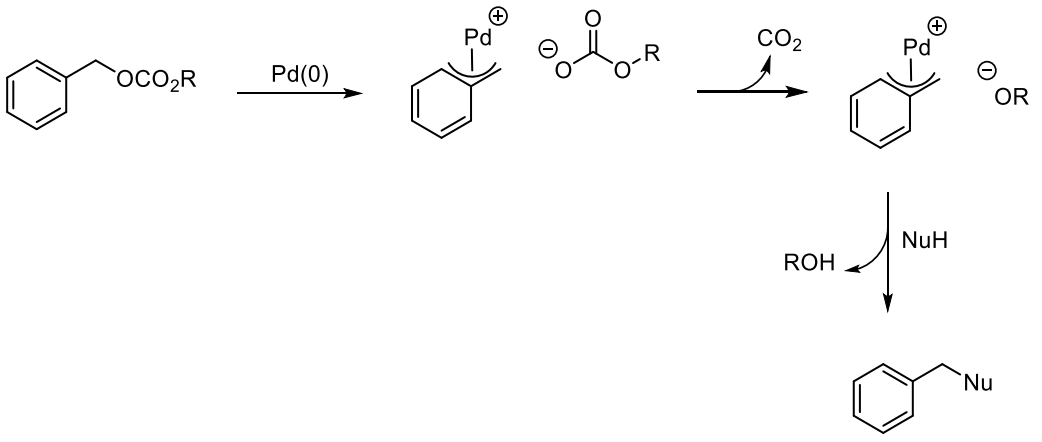


Scheme 1.12



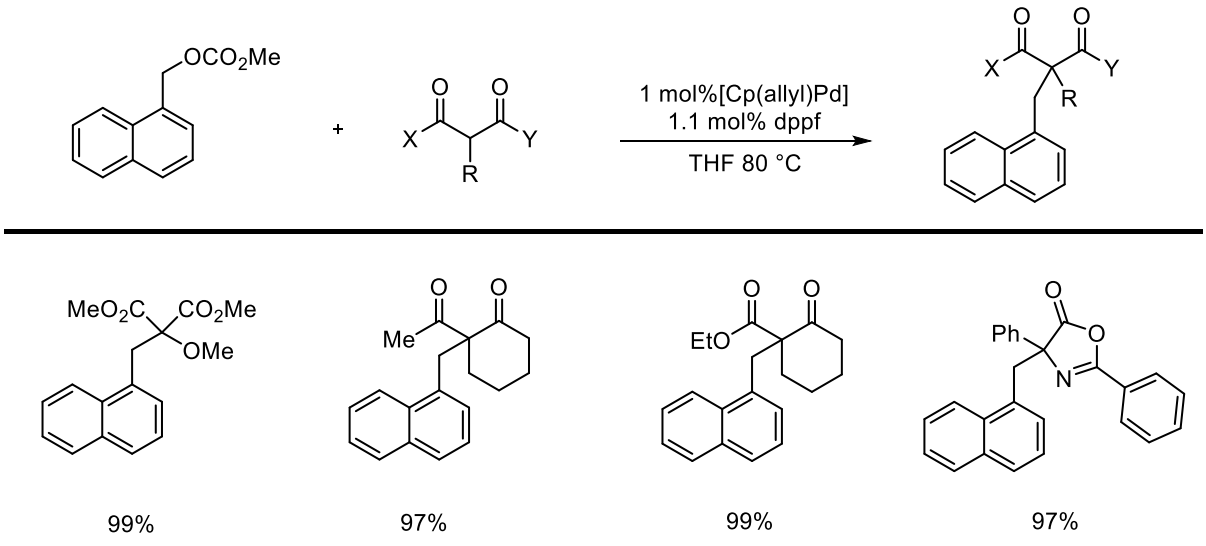
Scheme 1.13

Inspired by Tsuji's work,[20] Kuwano further expanded the benzylic alkylation to reactions performed under neutral conditions, without the use of an external base (Scheme 1.14).[3e, 4b] In this method, oxidative addition of benzyl carbonates to Pd(0), forms Pd-π-benzyl and carbonate intermediates. Under neutral conditions, decarboxylation of the carbonate intermediate generates the alkoxide *in situ*, which is expected to react as the base to generate the active nucleophile.



Scheme 1.14

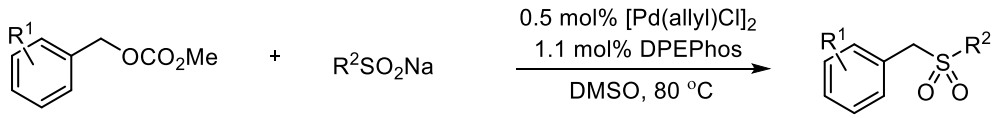
However, the [Pd(allyl)cod]BF_4, dppf catalyst/ligand system was unable to provide the benzylated product in the absence of a base (Scheme 1.12). It was assumed that in the absence of an external base the dppf-[Pd(allyl)cod]BF_4 complex is not reduced to the active Pd(0) catalyst precursor. However, when the catalyst/ligand combination was changed to dppf-[Cp(allyl)Pd] system, the benzylation was successful. This may arise from the facile formation of Pd(0) species from the (cyclopentadienyl)Pd(II) [Cp(allyl)Pd], as [Cp(allyl)Pd] is known to readily form Pd(0) species in the presence of tertiary phosphines via reductive elimination.[21] A variety of active methines: e.g. mono-substituted malonates, β-keto esters, 1,3-diketones and azlactones underwent palladium-catalyzed benzylic alkylation with (naphthyl)methyl carbonates in the presence of dppf-[Cp(allyl)Pd] (Scheme 1.15).[3e] This method could also be extended to benzyl carbonates when the reaction was carried out in the presence of 10 mol% of cyclooctadiene (cod) in order to suppress the aggregation of the Pd(0), which results due to the low reactivity of benzyl carbonates.[3e]

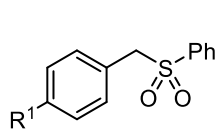


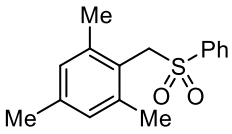
Scheme 1.15

Kuwano further extended the scope of the catalytic benzylic alkylation to arenesulfinates (pK_a ~ 7).[4b] In the presence of $[Pd(allyl)Cl]_2$ and DPEphos or dppf, benzyl carbonates underwent nucleophilic substitution by sodium arenesulfinates to generate benzylic sulfones in good yields (Scheme 1.16). The reaction tolerates both electron rich and electron deficient benzyl esters as well as various substituents on the phenyl ring of the arenesulfinates.

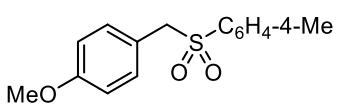
A plausible mechanism for the benzylation of arenesulfinates is shown below (Scheme 1.17). In the presence of catalytic Pd(0), benzyl carbonates undergo oxidative addition to Pd(0), generating (η^3-benzyl)palladium and carboxylate intermediates. Upon decarboxylation a methoxide anion is generated *in situ*. However, the nucleophilic attack of the softer arenesulfinates on to the (η^3-benzyl)palladium intermediate is kinetically favored.



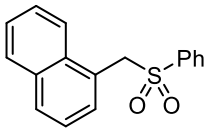




89%, 48 h



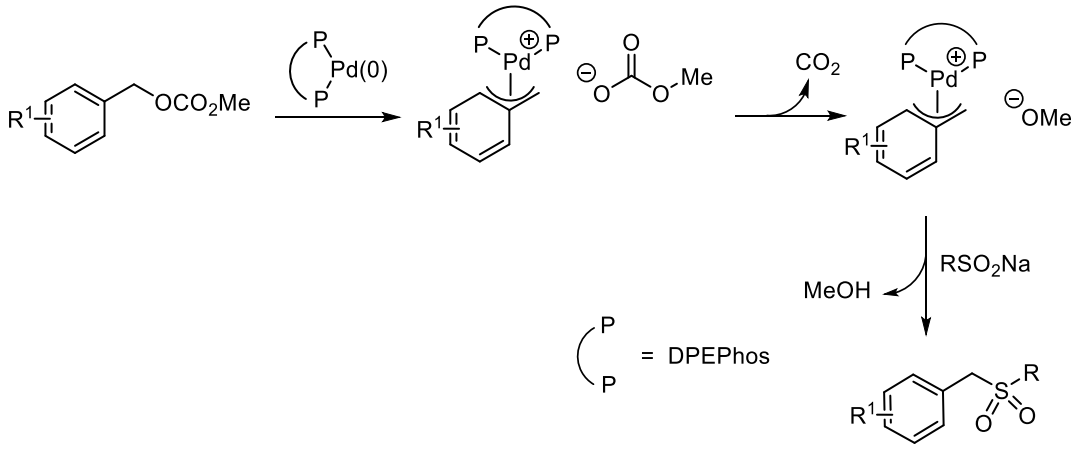
95%, 1 h



95%, 1 h

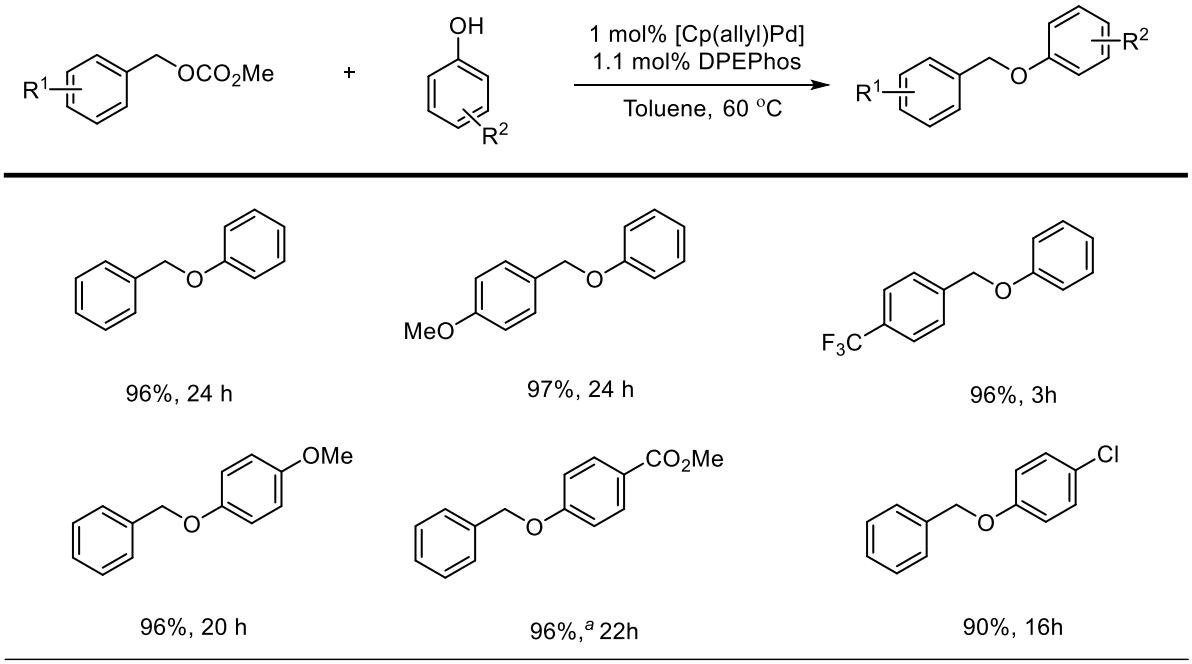
R^1	Yield	time/ h
H	95	1
OMe	89%	3
Cl	90%	24
CO_2Me	92%	1

Scheme 1.16



Scheme 1.17

In 2008, Kuwano reported the palladium-catalyzed benzylation of phenols (pK_a ~ 10) as a method for benzyl protection of phenols under neutral, base-free conditions (Scheme 1.18).[4a] Similar to the catalytic benzylic substitutions by arenesulfinates, benzyl methyl carbonates underwent benzylic substitution with phenols in the presence of [Cp(allyl)Pd] and DPEphos to provide benzyl ethers. However, they did not observe the formation of benzyl methyl ethers via the nucleophilic attack of methoxide on to η^3-Pd-benyl intermediate. This may arise from higher reactivity of the softer phenoxide anion with the soft η^3-Pd-benzyl intermediate compared to the harder methoxide. Electron rich (*p*-OMe) as well as electron poor (*p*-CF_3) benzyl methyl carbonates provided benzyl ethers in good yields. Remarkably, the electron poor *p*-trifluoromethyl benzyl methyl carbonate also provided the benzyl ether in 96% yield in 3 hours. However, with electron deficient phenols a 5 mol% catalyst loading was required to achieve complete conversion to the benzyl ether.



[a] At 5 mol% $[Pd(allyl)Cl]_2$ and 5.5 mol% DPEphos

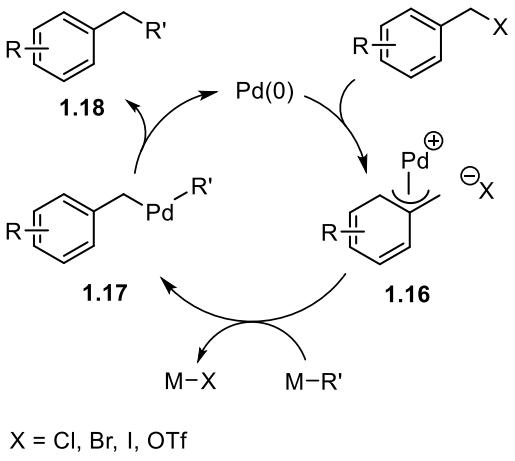
Scheme 1.18

1.4 Palladium-catalyzed decarboxylative benzylation

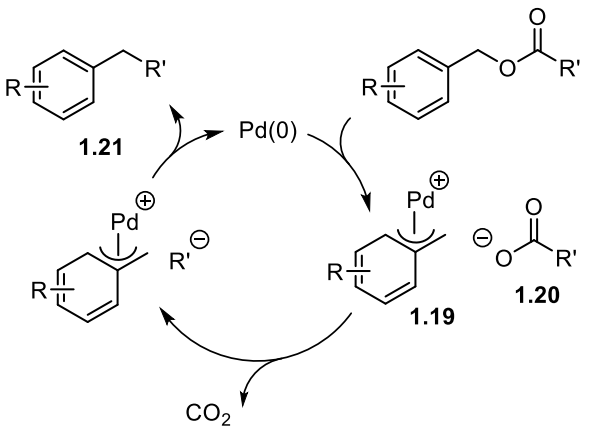
Palladium-catalyzed benzylic substitution reactions are generally limited to "soft" nucleophiles with pK_a's <20. Benzylation of less stabilized nucleophiles (pK_a >20), is more challenging, thus, requires strongly basic conditions or preformed organometallics. More often, preformed organometallics of indium,[22] gold,[23] zinc,[24] magnesium,[25] tin[6a] and boron[26] are used in benzylic cross-coupling reactions. Despite their enormous utility in cross-coupling reactions, preformed organometallic reagents may subject the substrates to highly basic conditions and ultimately generate stoichiometric quantities of metal salt waste. Catalytic decarboxylative coupling is an alternative method to standard cross-coupling reactions, where the transmetalation step is circumvented through decarboxylative metalation. Therefore, preformed organometallics are not required. Additionally, most benzylic coupling reactions utilize benzyl halides, which are

highly toxic, as the electrophilic coupling partner. In decarboxylative coupling, carboxylic acid derivatives are used as the starting material, and these can be easily synthesized from respective benzyl alcohols that are comparatively less toxic.

The catalytic cycle for a standard cross-coupling reaction is shown in Scheme 1.19. The oxidative addition of the benzyl halide to Pd(0) generates the Pd(II) intermediate (**1.16**), which will undergo transmetalation to provide the intermediate (**1.17**), and this will reductively eliminate to provide the benzylated product (**1.18**).



Scheme 1.19



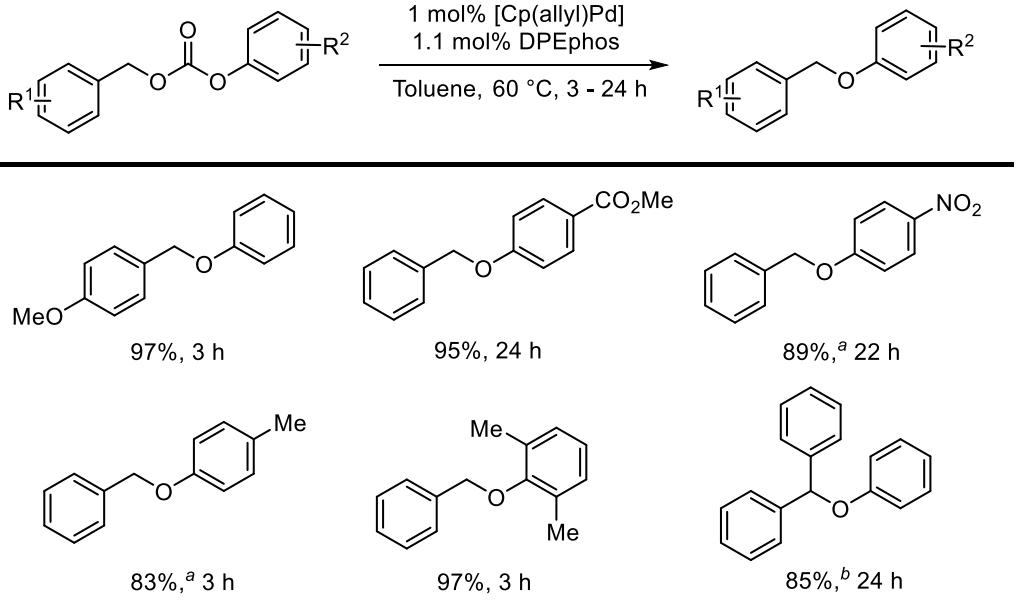
Scheme 1.20

In a typical decarboxylative cross-coupling reaction (Scheme 1.20), oxidative addition of the carboxylic acid derivative to Pd(0) generates Pd(II)-**1.19** and the carboxylate intermediate (**1.20**). Generally oxidative addition is followed by decarboxylation to generate the nucleophile under neutral conditions. Depending on the nature of the nucleophile it will attack the η^3-benzyl-Pd intermediate via an inner sphere or outer sphere mechanism to generate the benzylated product (**1.21**). Moreover, carbon dioxide is the only by-product formed in this cross-coupling reaction. Therefore, catalytic decarboxylative cross-coupling reactions are much greener compared to

standard cross-coupling reactions. However, palladium-catalyzed decarboxylative benzylation reactions are still in their infancy compared to the catalytic decarboxylative allylation reactions.

1.4.1 Decarboxylative benzylation of phenols

Kuwano and Kusano reported the first catalytic decarboxylative benzylation reaction in 2008,[4a] in which aryl benzyl carbonates delivered aryl benzyl ethers in the presence of [Cp(allyl)Pd] and DPEphos (Scheme 1.21). Some electron deficient aryl benzyl carbonates required either a high catalyst loading or a longer reaction time for the completion of the reaction, while electron rich substrates provided very high yields in less time and lower catalyst loading.

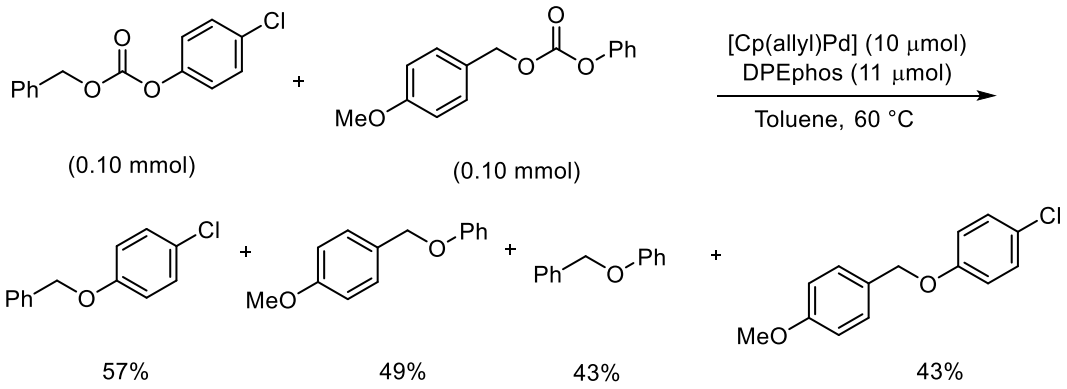


[a] Reaction was conducted on a 0.2 mmol scale with 5 mol% catalyst loading, [b] Reaction was conducted with 2 mol% catalyst loading, by using dppf in place of DPEphos

Scheme 1.21

The formation of crossover products from a 1:1 mixture of aryl benzyl carbonates was highlighted to support a mechanism involving an η^3-benzyl-Pd and phenoxide ion pair rather than

an η^1-benzyl-Pd intermediate (Scheme 1.22). However, the possibility of generating cross-over products due to oxidative addition cannot be ruled out.



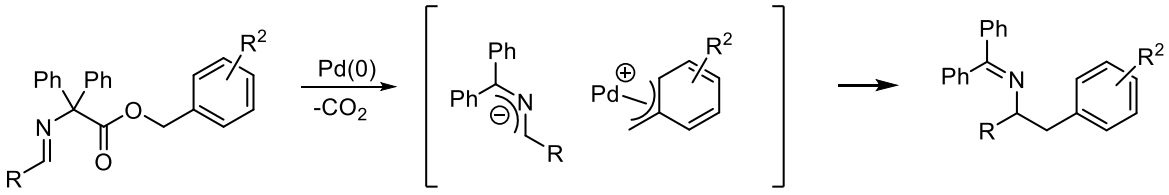
Scheme 1.22

1.4.2 Decarboxylative benzylation of diphenylglycinate imines

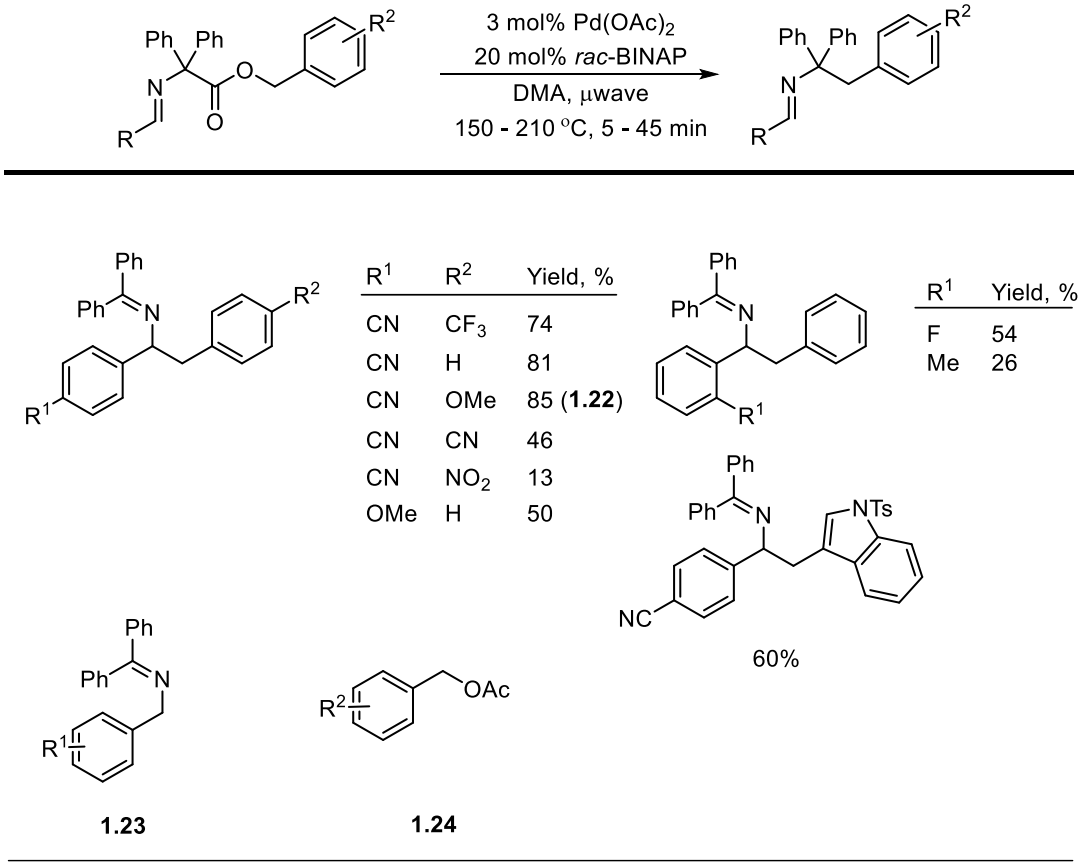
Further studies on palladium-catalyzed decarboxylative benzylation were performed by Fields and Chruma utilizing benzyl diphenylglycinate imines.[27] This work highlighted the use of a less stabilized, non-enolate carbon nucleophile in catalytic decarboxylative benzylation for the first time.

In the presence of palladium acetate and racemic BINAP, a variety of benzyl diphenylglycinate imines underwent decarboxylative benzylation under microwave conditions, to deliver homobenzylic imines (Scheme 1.23). Similar to the respective decarboxylative allylation of α-imino anions,[28] decarboxylative benzylation occured regioselectively at the least hindered carbon of the 2-azaallyl anion. While a *p*-CF_3 substituent on the benzyl ester provided relatively high yields, *p*-NO_2 and *p*-CN substituents on the benzyl ester moiety greatly reduced the yields (Scheme 1.24). The higher yield obtained with **1.22** could be attributed to the stabilization of the cationic

η^3-Pd-benzyl intermediate by the presence of an electron donating *p*-OMe substituent on the phenyl ring, and the stabilization of the 2-azaallyl anion by the presence of the electron withdrawing -CN group. The major side products of this decarboxylative cross-coupling reaction arose either via the decarboxylative protonation of the azaallyl anion (**1.23**), or via the competitive nucleophilic addition of acetate to the η^3-Pd-benzyl intermediate (**1.24**).



Scheme 1.23

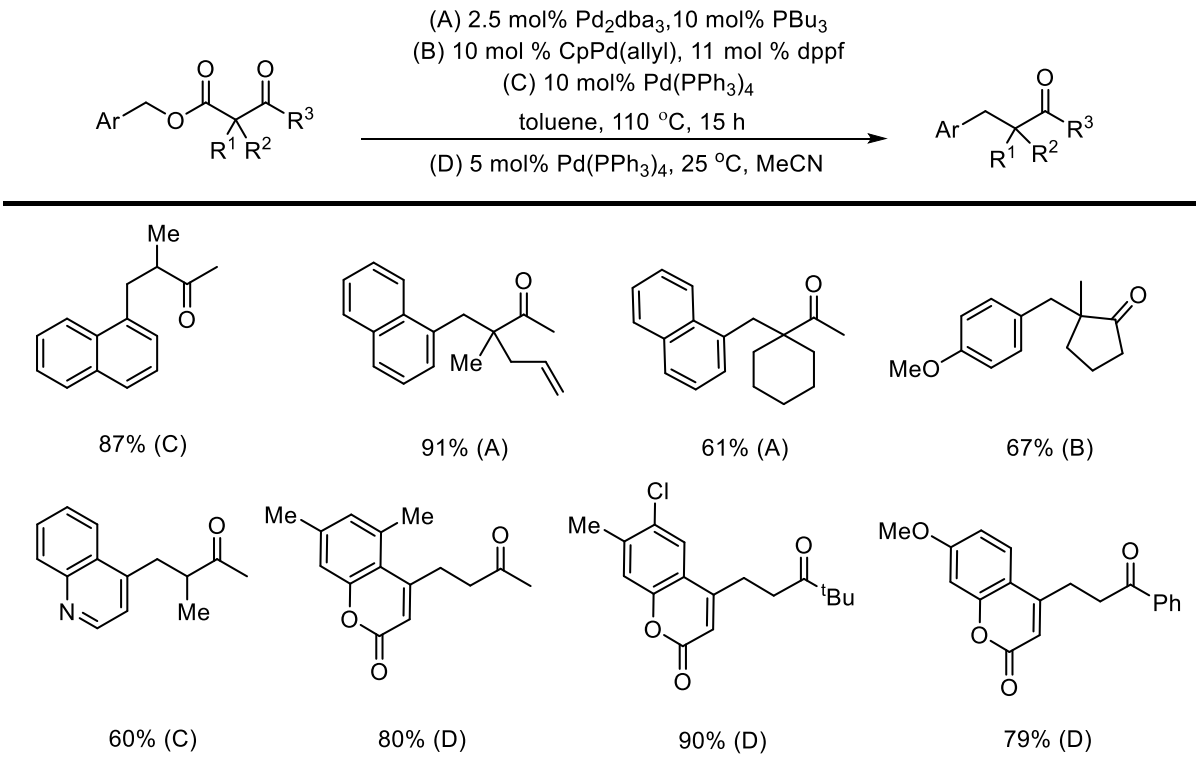


Scheme 1.24

1.4.3 Decarboxylative benzylation of ketones

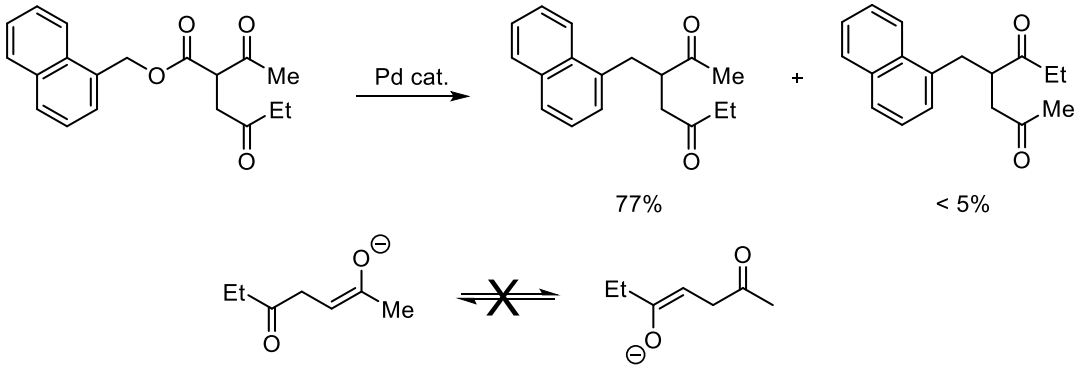
Extension of the nucleophile scope of the decarboxylative benzylic cross-coupling to ketone enolates (pK_a ~ 20) and acetylide (pK_a ~ 25) nucleophiles was reported by Tunge *et al*. in 2010.[29] The work on decarboxylative cross-coupling of benzyl β-keto esters was analogous to the decarboxylative coupling of allyl β-keto esters.[30] However, this was the first report of decarboxylative coupling of an enolate with a benzyl electrophile (Scheme 1.25).

In this work, benzyl β-ketoesters underwent decarboxylative cross-coupling in the presence of a more electron deficient dba-ligated palladium with smaller electron rich ligands, for example PBu_3. Additionally, CpPd(allyl)-dppf, and $Pd(PPh_3)_4$ were also successful catalysts. However, benzyl β-ketoesters were mostly limited to aryl and heteroaryl systems that have extended π-conjugation.



Scheme 1.25

Similar to the decarboxylative allylation of enolates, decarboxylative benzylation of enolates is also highly regiospecific. Moreover, the new C–C bond formation occurs at the site of decarboxylation without enolate isomerization (Scheme 1.26). From a synthetic standpoint this result is interesting, because catalytic decarboxylation allows one to generate non-stabilized enolates that are difficult to generate via standard acid-base chemistry. The proposed catalytic cycles involved in decarboxylative coupling of α-mono and α,α-disubstituted enolates to the allyl/benzyl electrophiles will be discussed in detail in Chapter 3.



Scheme 1.26

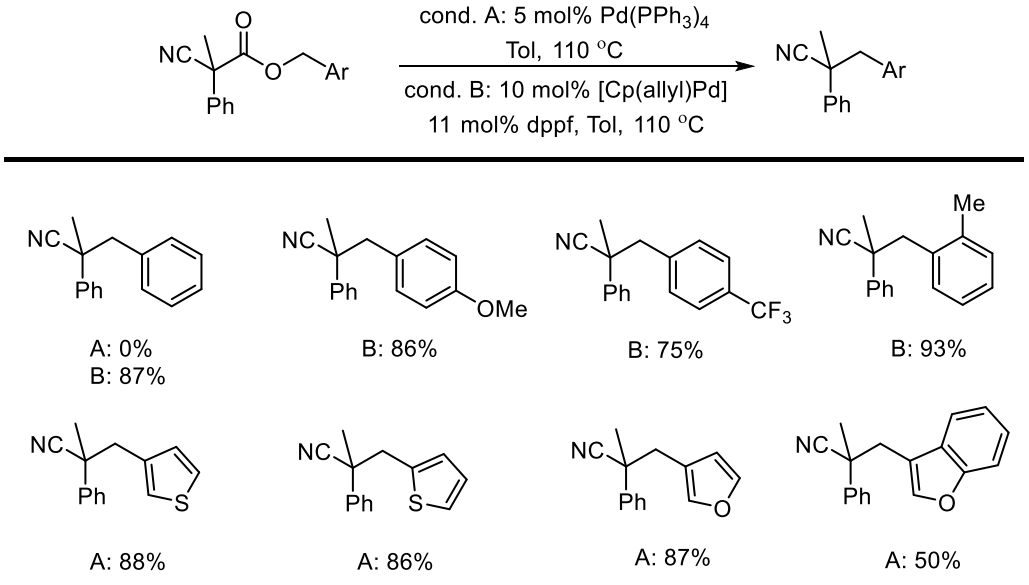
1.4.4 Decarboxylative benzylation of alkynes

Palladium-catalyzed decarboxylative benzylation of alkynes will be discussed in detail in Chapter 2.

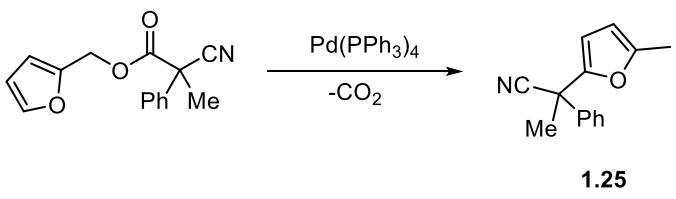
1.4.5 Decarboxylative benzylation of nitriles

After the seminal report on decarboxylative benzylation of alkynes and ketones, Recio III (a former co-worker of the Tunge group) demonstrated the synthesis of benzyl nitriles via the decarboxylative benzylation of benzyl cyanoacetates (DMSO pK_a ~ 22-33).[31] Initial screening of

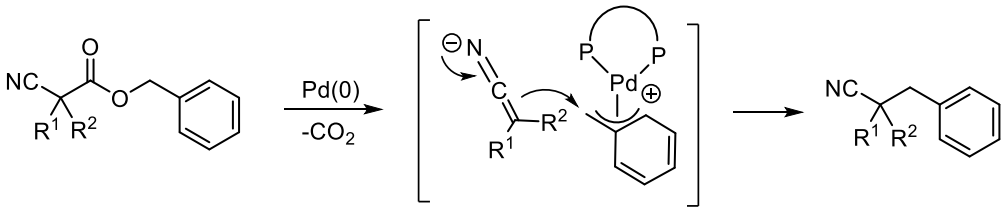
benzyl cyanoacetates with 5 mol% $Pd(PPh_3)_4$ delivered protonated nitriles, NCCH(Me)Ph. Changing to [Cp(allyl)Pd] and dppf, a catalyst/ligand combination, which previously successfully reacted with simple benzyl ester derivatives,[3e] also successfully coupled benzyl cyanoacetates to provide benzyl nitriles in good yields (Scheme 1.27). Most of the heteroaromatic methyl esters also provided heteroaryl methyl nitriles with 5 mol% $Pd(PPh_3)_4$, with the exception of α,α-disubstituted 2-methyl furanyl cyanoacetates, which provided the arylated product **1.25** (Scheme 1.28). (The ligand-dependent selectivity of α,α-disubstituted 2-methyl furanyl cyanoacetates to deliver benzylated vs arylated nitriles will be discussed in Chapter 4). In the presence of a bidentate ligand, the decarboxylative coupling of benzyl cyanoacetates occured via an outer-sphere mechanism, due to the lack of a vacant coordination site on palladium (Scheme 1.29).



Scheme 1.27



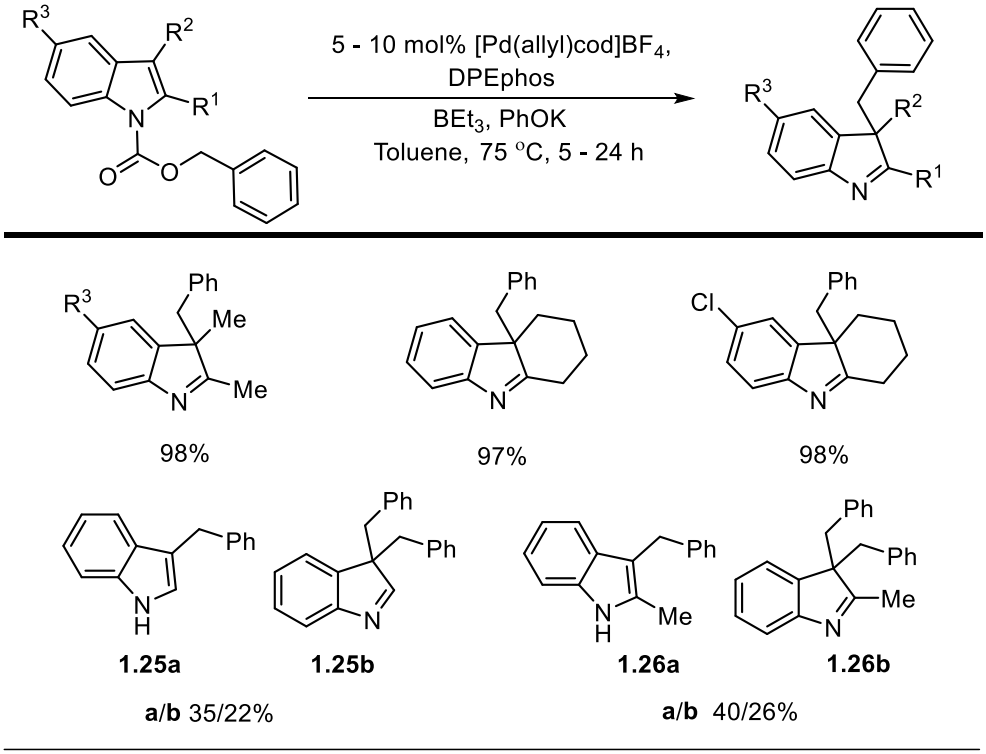
Scheme 1.28



Scheme 1.29

1.4.6 Decarboxylative benzylation of *N*-Cbz indoles

Recently, Rawal and co-workers reported the decarboxylative coupling of *N*-Cbz indoles to deliver functionalized indolenines via the C3-benzylation of indoles (Scheme 1.30).[32]



Scheme 1.30

The C3-benzylation of indoles via standard methods imposes a significant challenge due to the formation of N and C3-alkylated products under basic conditions. In this work, C3-substituted *N*-

Cbz indoles underwent decarboxylative benzylation in the presence of [Pd(allyl)cod]BF_4 and DPEphos to generate benzylic indolenines with a quaternary carbon at C3. However, C3-unsubstituted *N*-Cbz indoles delivered a mixture of mono- (**1.25a** and **1.26a**) and di-benzylated products (**1.25b** and **1.26b**). It is also noteworthy that the addition of triethyl borane to the reaction mixture accelerated the benzylation reaction.

In summary, the scope of the nucleophiles that engage in catalytic decarboxylative benzylic cross-coupling reactions is limited compared to the breadth of nucleophiles that participate in decarboxylative allylations. Therefore, further research is necessary to implement new decarboxylative benzylation reactions. Moreover, there are no asymmetric decarboxylative benzylations reported although such reactions could be useful for the synthesis of molecules that contain enantioenriched 1,1-diarylmethane motifs. In addition to decarboxylative benzylations, reports on decarboxylative arylations have also started to appear in literature.[31, 33] The next few chapters highlight our work towards the development of racemic, as well as asymmetric decarboxylative benzylic alkylation, as well as decarboxylative arylation and dearomatization reactions.

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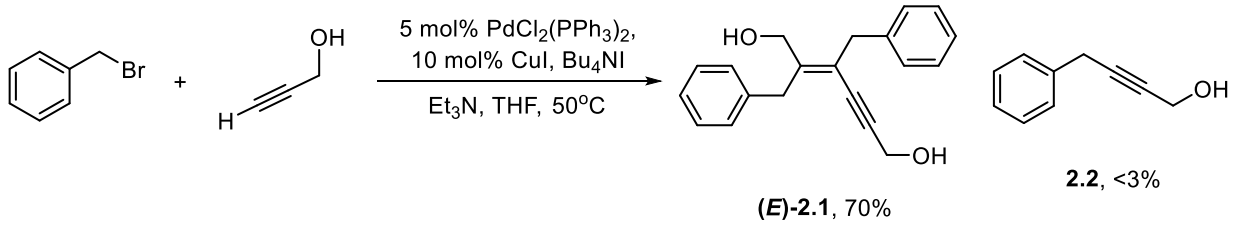
Chapter 2

Palladium-Catalyzed Decarboxylative Benzylation of Alkynes

This work was developed by Robert R. P. Torregrosa, a former coworker in the Tunge group, in conjunction with contributions from this author. With the concern for a clear and comprehensive discussion of the subject, all the results will be presented herein; results from this author will be denoted with an asterisk (*).

2.1 Introduction

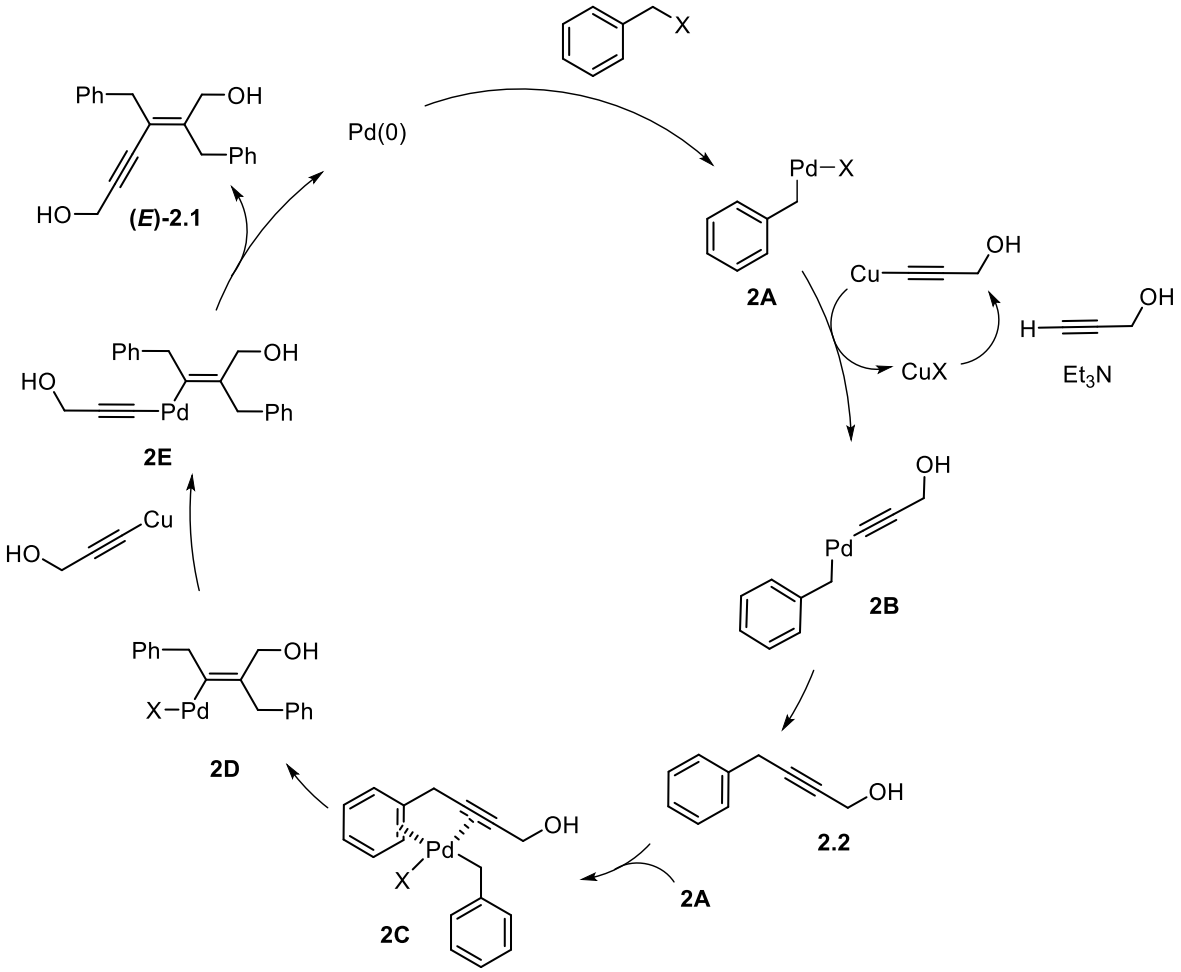
Alkynes are of enormous synthetic value due to their versatility in numerous transformations.[1] Therefore, developing methods to incorporate an alkyne moiety into organic molecules has been a long-standing goal in organic synthesis.[2] While Sonogashira coupling is the most widely used method to couple an sp^2 carbon (e.g. aryl and alkenyl halides or triflates) with alkynes, the coupling of sp^3 carbon centers (e.g. alkyl and benzyl halides) with alkynes under standard Sonogashira conditions has proven difficult.[3] For example, alkynylation of benzyl halides under palladium/copper-catalyzed conditions can result in further coupling of benzyl alkynes (Scheme 2.1).[3b] A tandem Sonogashira-carbopalladation-Sonogashira sequence has been proposed for the formation of conjugated enyne (*E*)-**2.1**, and the expected benzyl alkyne **2.2** is generated in a very low yield.



Scheme 2.1

The proposed catalytic cycle for the formation of (*E*)-**2.1** is as follows. The oxidative addition of benzyl halide to Pd(0) generates the palladium(II)-benzyl intermediate **2A**. The oxidative addition step is immediately followed by transmetalation with the *in-situ* generated copper-acetylide to generate complex **2B**. Reductive elimination of **2B** yields the benzyl alkyne **2.2**. At this stage the coordination of a second Pd(II)-benzyl complex to **2.2** (**2C**) is thought to facilitate the formation of σ-vinyl-palladium(II) complex (**2D**) via carbopalladation. Transmetalation of **2D**

with a second copper-acetylide and subsequent reductive elimination of **2E** leads to enyne (*E*)-**2.1** and regenerates the Pd(0) species.

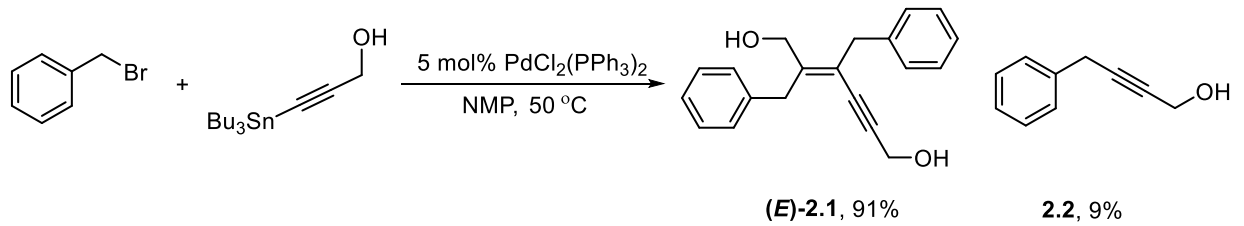


Scheme 2.2

Similarly, efforts to couple benzyl halides with alkynyltributyltin via the Stille coupling have also failed due to the formation of enyne (*E*)-**2.1** via a Stille-carbopalladation-Stille sequence (Scheme 2.3).[4]

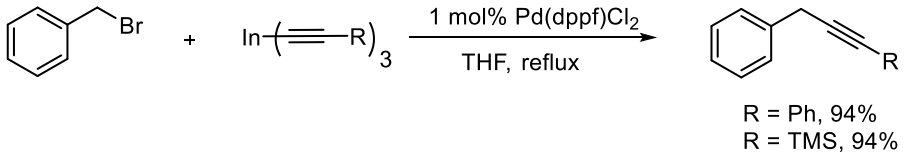
The first successful coupling of benzyl halides with alkynyl organometallics was reported by Sarandeses and coworkers using a trialkynylindium reagent and catalytic palladium (Scheme 2.4).[5]

For this transformation it was necessary to pre-synthesize the trialkynylindium reagent by treating $InCl_3$ with alkynyl Grignard or lithium reagents, which was stored in THF to prevent decomposition. Due to the three alkynyl groups attached to the metal, cross-coupling could be carried out using substoichiometric quantities of trialkynylindium (34 mol%) to provide benzyl alkynes in a high yield.



(*E*)-**2.1**, 91% **2.2**, 9%

Scheme 2.3

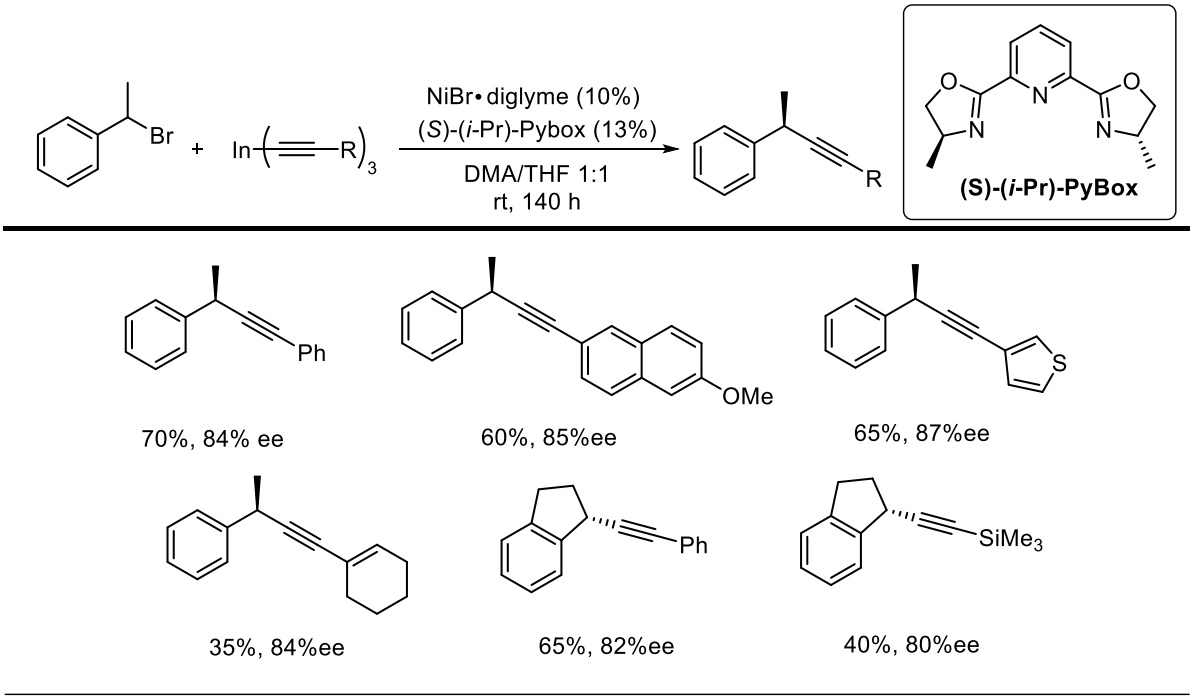


Scheme 2.4

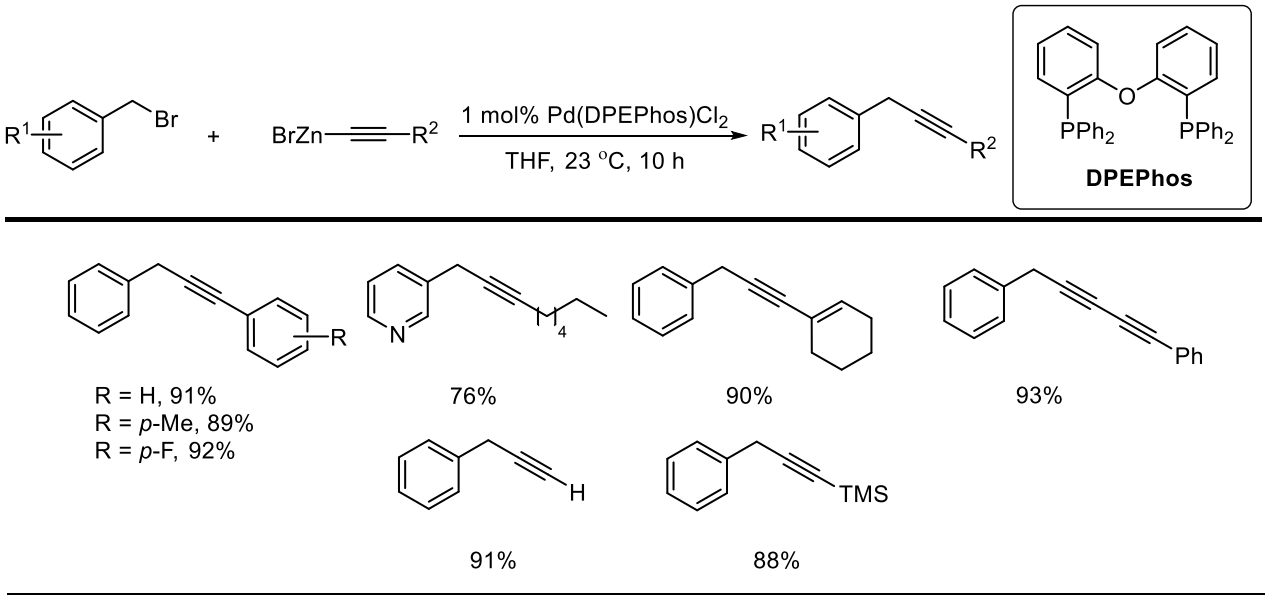
In a later study, Sarandeses and coworkers reported a nickel-catalyzed enantioselective coupling of secondary benzyl halides with trialkynylindiums to provide benzyl alkynes in moderate yield and good ee (Scheme 2.5).[6] Thus far, this is the only method reported for the asymmetric coupling of secondary benzyl halides with alkynyl organometallics.

In 2005, Negishi reported the use of alkynylzinc reagents for the palladium-catalyzed coupling of benzyl halides with alkynes (Scheme 2.6).[7] In the presence of Pd(DPEphos)Cl_2 and alkynylzinc, benzyl alkynes were synthesized in good to excellent yields at room temperature. Additionally, this work demonstrates the coupling of a broad scope of alkynylzinc reagents, in which alkynylzinc

bromides bearing aryl, alkyl, alkenyl, alkynyl, H and trimethylsilyl could be coupled. However, this method is only limited to primary benzyl halides.

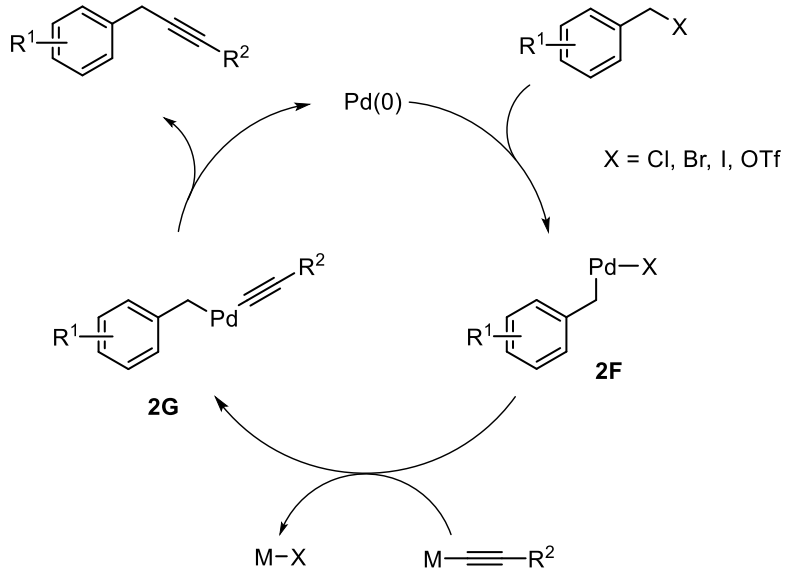


Scheme 2.5



Scheme 2.6

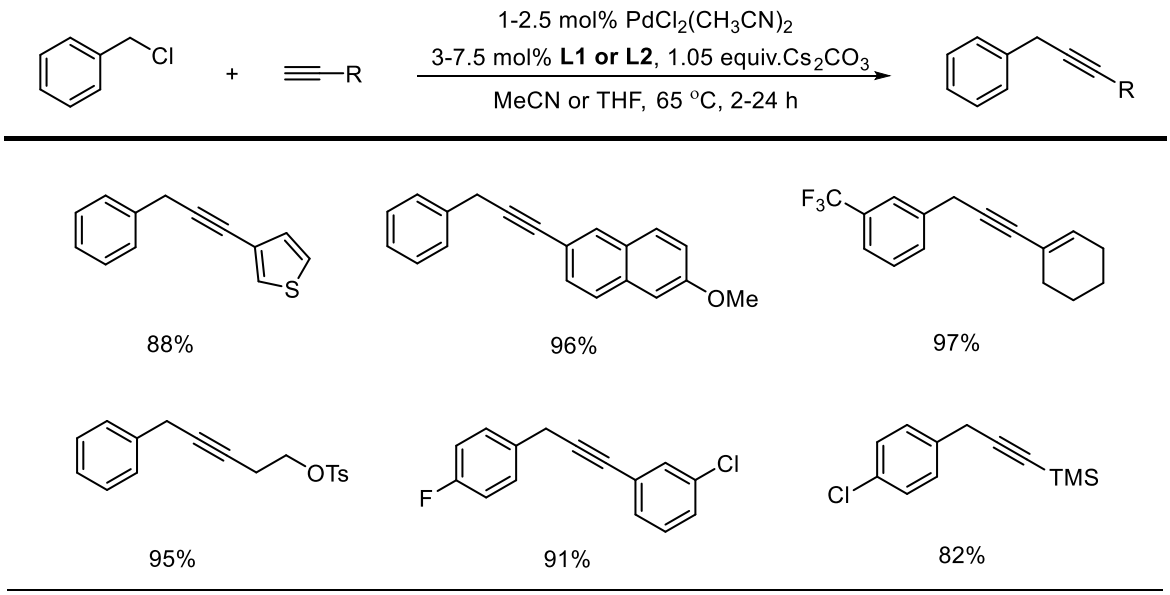
A generalized catalytic cycle for the palladium-catalyzed coupling of benzyl halides to preformed alkynyl organometallics is illustrated in Scheme 2.7. The initial oxidative addition of benzyl halide to Pd(0) generates benzyl-Pd(II) adduct **2F**, in which transmetalation with preformed alkynyl organometallics leads to the formation of **2G**. Reductive elimination of **2G** provides the benzyl alkyne.



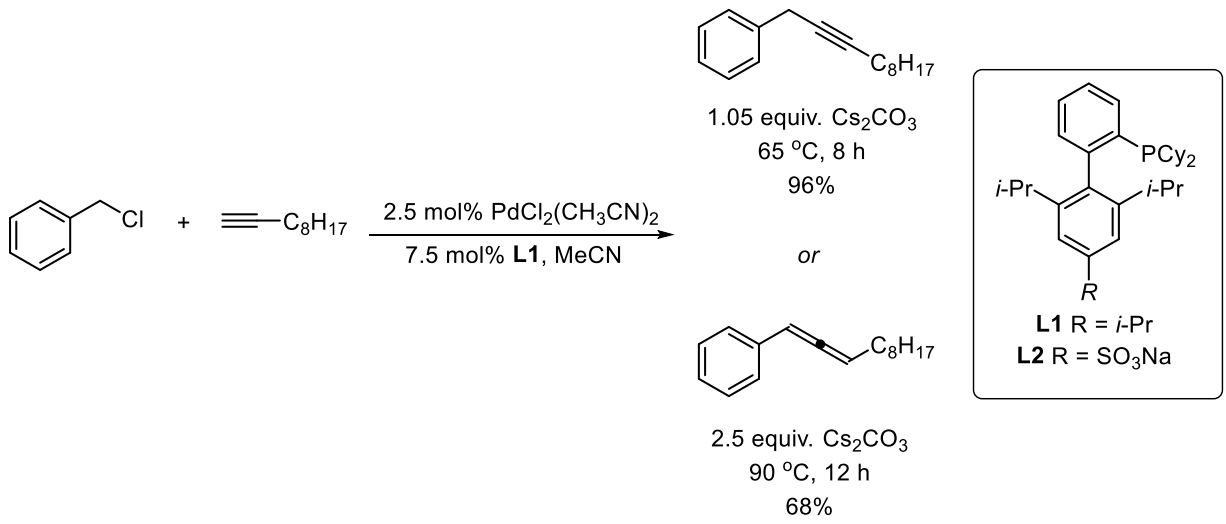
Scheme 2.7

Alkynylation of benzyl halides required the use of alkynyl organometallics until Buchwald's development of a Heck alkynylation protocol that uses base to generate metal acetylides *in situ* (Scheme 2.8).[8] The authors used $PdCl_2(CH_3CN)_2$ and a monodentate phosphine ligand (**L1** or **L2**), and hypothesized that electron-rich bulky phosphine ligands disfavor the coordination of benzyl alkynes to Pd(II) to preventing the enyne formation like was previously observed (e.g. Scheme 2.3). While lower temperatures yielded benzyl alkynes in moderate to good yields, longer reaction times and higher temperatures favored the isomerization of benzyl alkynes to allenes. Additionally, excess loading of Cs_2CO_3 also facilitated the formation of allene (Scheme 2.9). Therefore, for

some substrates a shorter reaction time and the change of solvent were necessary to prevent the isomerization of alkynes to allenes. Additionally, this method was also limited to primary benzyl halides.



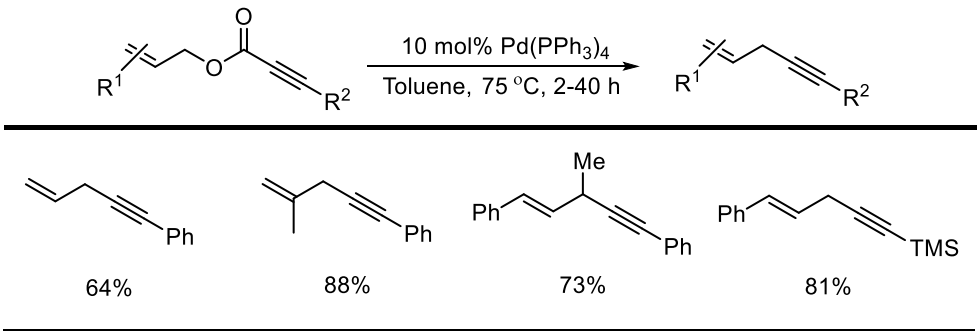
Scheme 2.8



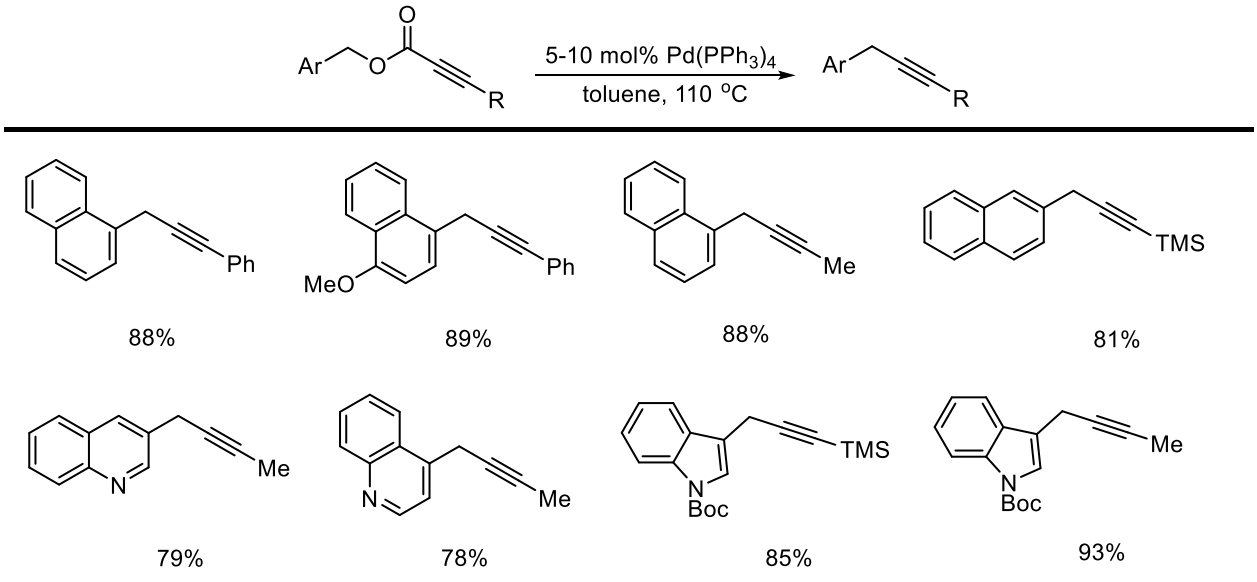
Scheme 2.9

Following their work on allyl-acetylide coupling (Scheme 2.10),[9] Tunge and coworkers extended their work to couple benzyl electrophiles with alkynes. Under palladium-catalyzed

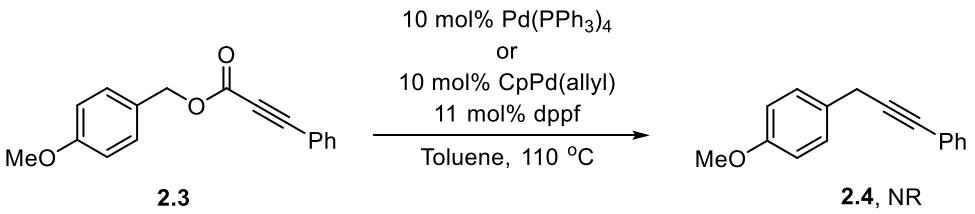
conditions benzyl esters of propiolic acids underwent decarboxylative benzylation to yield benzyl alkynes in good to high yields (Scheme 2.11).[10] Importantly, the decarboxylative coupling does not require strongly basic reagents or preformed organometallics. In addition, benzyl propiolates could be easily synthesized from the respective benzyl alcohols, therefore, the use of toxic benzyl halides could be avoided.[11] While this method exhibited a broad substrate scope, an extended π-system was required for coupling to occur. For example, benzyl ester **2.3** did not react under optimized conditions (Scheme 2.12).[11]



Scheme 2.10



Scheme 2.11

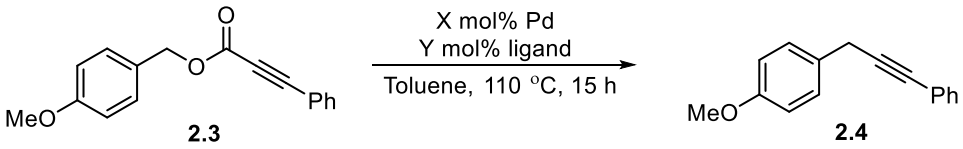


Scheme 2.12

2.2 Decarboxylative coupling of benzyl propiolic esters without extended π-systems

To implement a more generalized catalytic decarboxylative method for the synthesis of benzyl alkynes, former graduate student Robert Torregrosa screened benzyl propiolate **2.3** with different catalyst/ligand combinations to identify reaction conditions to yield **2.4**, (Table 2.1).

Table 2.1

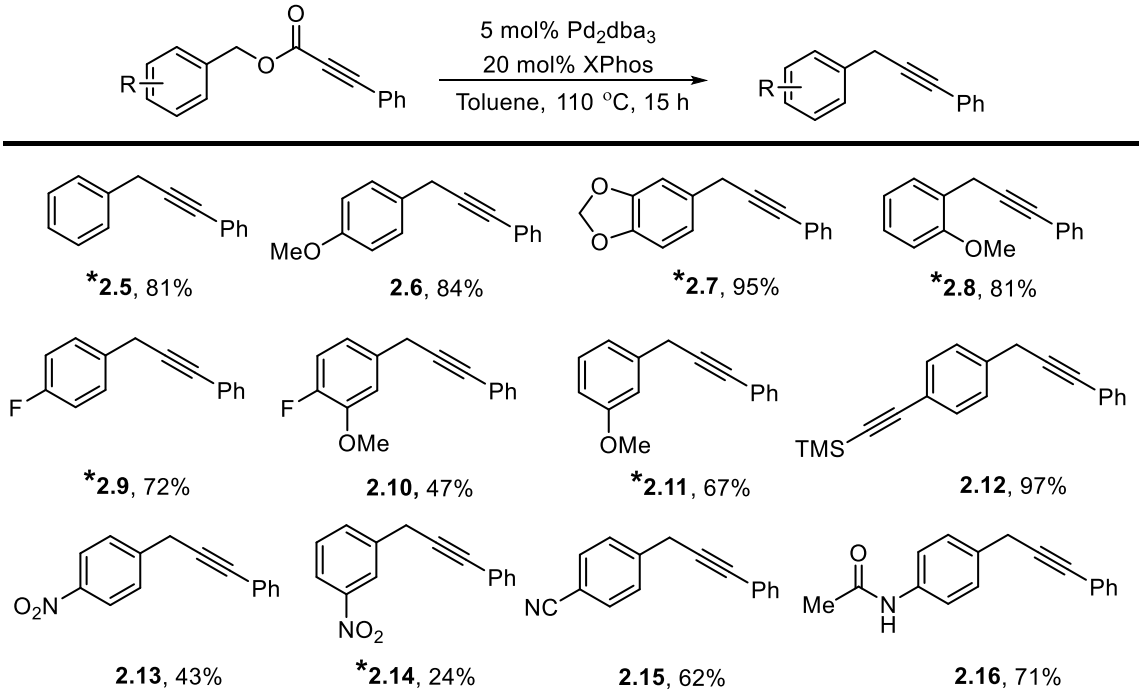


Entry	X	Pd source	Y	Ligand	%conversion[a]
1	10	CpPd(allyl)	11	dppf	0
2	10	CpPd(allyl)	11	dppe	0
3	10	CpPd(allyl)	11	Xantphos	0
4	10	CpPd(allyl)	20	PPh_3	0
5	10	CpPd(allyl)	20	PMe_3	67
6	10	CpPd(allyl)	20	PBu_3	47
7	10	CpPd(allyl)	20	$P(t\text{-}Bu)_3$	0
8	10	CpPd(allyl)	20	PCy_2bp	72
9	5	Pd_2dba_3	20	PCy_2bp	63
10	5	Pd_2dba_3	20	SPhos	77
11	5	Pd_2dba_3	20	XPhos	94
12	2.5	Pd_2dba_3	10	XPhos	11
13	1	Pd_2dba_3	5	XPhos	0

[a]Determined by ^1H NMR, performed by Robert Torregrosa.

While monodentate and bidentate phosphine ligands carrying PPh_n (n=2 or 3) failed to provide any coupling product (entry 1-4), changing to alkyl and more electron rich phosphine ligands led to the formation of **2.4**. A 94% conversion to **2.4** was observed when $Pd_2(dba)_3$ and Xphos were used (entry 11). Therefore, conditions used in entry 11 were chosen as the optimized reaction conditions.

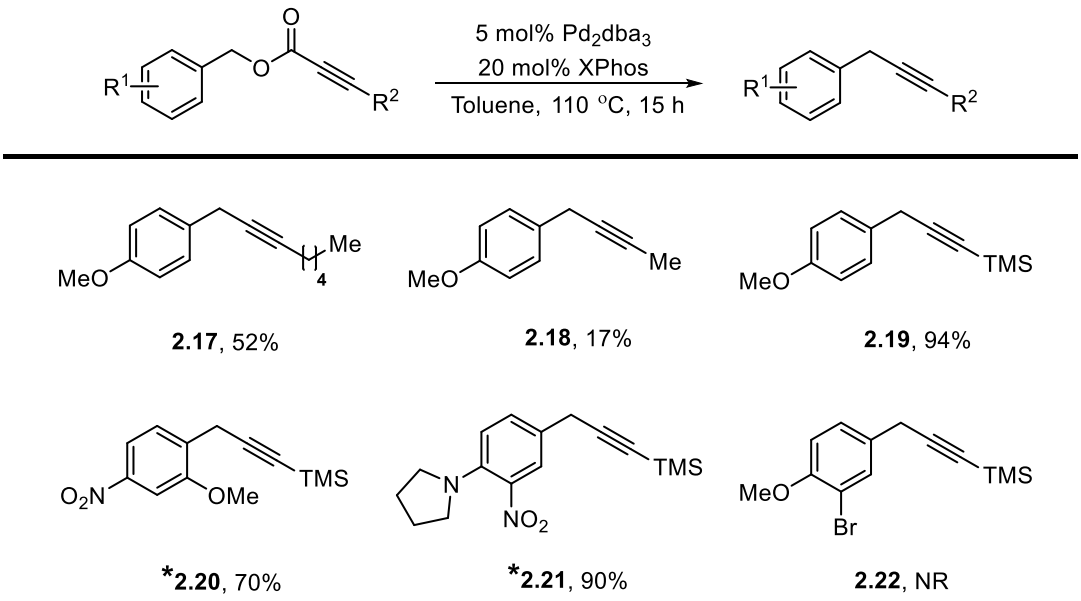
Next a variety of simple benzyl propiolates were synthesized and subjected to the optimized reaction conditions (Scheme 2.13). Whenever an electron donating substituent was present on the aryl moiety, benzyl alkynes were obtained in good to high yields, due to the stabilization of the Pd-π-benzyl intermediate. As expected electron withdrawing substituents lowered the yield of the reaction. While *para*-fluoro (**2.9, 2.10**) substituted propiolates underwent cross-coupling providing moderate yields of the benzyl alkynes, having a bromo substituent (**2.22**) shut down the reaction.



*Author contributed to the synthesis of benzyl phenyl propiolates.

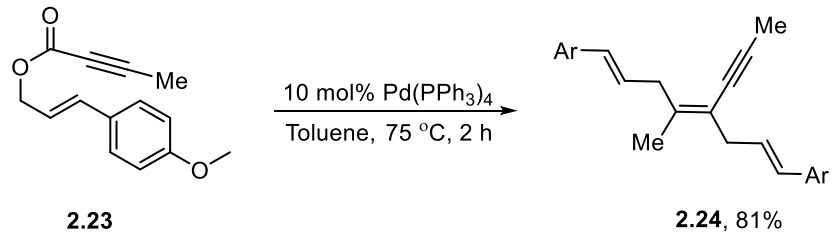
Scheme 2.13

Next we looked at the scope of the nucleophilic coupling partner (Scheme 2.14). Changing the phenyl acetylide to alkyl and trimethylsilyl acetylides was also tolerated. While bulky groups on acetylide, e.g. TMS, provided high yields of the coupling product, having a methyl acetylide (**2.18**) lowered the yield. However, the formation of dimeric products (**2.24**) was not observed with benzyl methyl propiolates as previously observed with **2.23** in allyl acetylide coupling.[9]



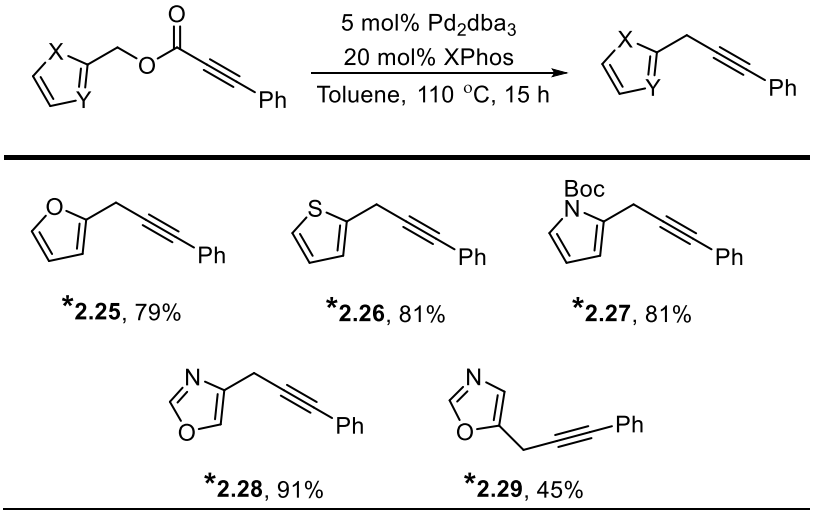
*Author contributed to the synthesis of benzyl trimethylsilyl propiolates.

Scheme 2.14



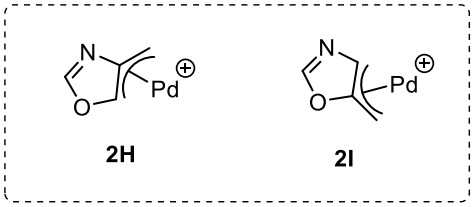
We also examined the reactivity of phenyl propiolates containing a heteroaryl moiety (Scheme 2.15). Phenyl propiolates having a furan (**2.25**), thiophene (**2.26**), pyrrole (**2.27**) and a 4-oxazole moiety (**2.28**), pleasingly provided the heteroarylmethyl alkynes in good to excellent yields, while

5-oxazole methyl alkyne (**2.29**) was obtained in a moderate yield. The difference in reactivity of **2.28** and **2.29** can be attributed to the higher resonance stabilization of **2H** over **2I.**

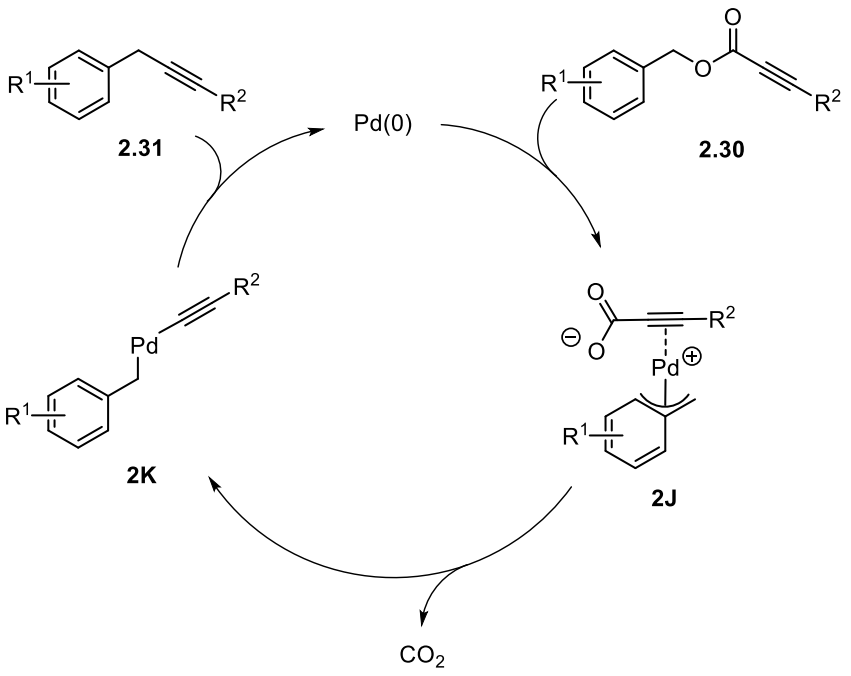


*Author contributed to the synthesis of heteroarylmethyl alkynes.

Scheme 2.15



The proposed catalytic cycle for the palladium-catalyzed decarboxylative benzylation of alkynes is outlined in Scheme 2.16. The oxidative addition of benzyl propiolate **2.30** to Pd(0) generates the Pd-π-benzyl carboxylate intermediate **2J**. The coordination of alkyne to the Pd(II)-benzyl complex in **2J** is thought to facilitate the decarboxylation. Upon decarboxylation the formation of Pd-bound acetylide intermediate **2K** is hypothesized.[9] Finally, the reductive elimination of **2K** yields the benzyl alkyne **2.31**.



Scheme 2.16

In summary, we have been able to expand the previously reported decarboxylative benzylic coupling of alkynes to benzyl systems that do not have extended π-conjugation. With the increased substrate scope, palladium-catalyzed decarboxylative coupling can be used as a general method for the coupling of primary benzyl electrophiles to alkynes. Moreover, compared to traditional cross-coupling reactions palladium-catalyzed decarboxylative couplings offer a greener synthesis producing CO_2 as the sole byproduct, while avoiding pre-formed organometallics or basic additives.

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Appendix A1

General Information:

All glassware were oven or flame dried prior to use. All reactions were run under an argon atmosphere using standard Schlenk techniques or an inert atmosphere glove box. All palladium catalysts and ligands were purchased from Strem and stored in the glove box under an argon atmosphere. Toluene and THF were dried over sodium and distilled in the presence of benzophenone. Dried toluene was taken to the glove box in a Schlenk flask with activated molecular sieves. CH_2Cl_2 was dried over alumina. Other commercially available solvents were used without additional purification. Compound purification was effected by flash chromatography using 230x400 mesh, 60Å porosity silica obtained from Sorbent Technologies. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer equipped with a QNP cryoprobe and referenced to residual protio solvent signals. Structural assignments were based on ^1H, ^{13}C, DEPT-135, COSY, NOESY and HSQC. Mass spectrometry was run using EI or ESI techniques.

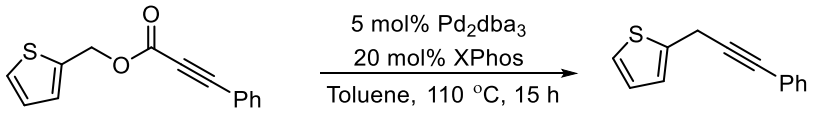
Synthesis of primary benzyl alcohols:

Primary benzyl alcohols were synthesized either via the reduction of benzaldehydes using sodium borohydrides or reduction of benzoic acids using $LiAlH_4$.

Representative procedure for the synthesis of benzyl propiolates:

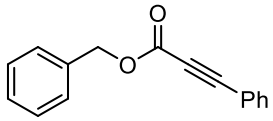
Racemic propiolic esters were prepared by standard DCC, DMAP coupling as outlined in literature.[1]

Representative procedure for the palladium-catalyzed decarboxylative benzylation of alkynes:



In a glove box, under an argon atmosphere, a flame dried Schlenk tube with a stir bar was charged with propiolic ester (60 mg, 0.25 mmol), $Pd_2(dba)_3$ (11.3 mg, 0.012 mmol), XPhos (23.5 mg, 0.05 mmol) and toluene (6 mL). The Schlenk tube was equipped with a septum and the sealed tube was removed from the glove box and stirred at 110 °C for 15 hours. The resulting reaction mixture was cooled to room temperature and concentrated *in vacuo* and was purified via flash chromatography over silica gel.

Characterization data for benzyl propiolates:



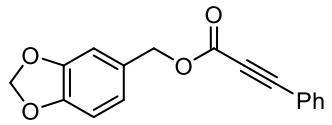
benzyl 3-phenylpropiolate (SM-1-109)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.55 (m, 2H), 7.41 (tdd, *J* = 15.2, 10.9, 7.8 Hz, 8H), 5.27 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.10, 135.07, 133.21, 130.88, 128.86, 128.82, 128.75, 119.70, 86.91, 80.65, 67.91.

HRMS calcd for $C_{16}H_{12}O_2Na$ [M+Na] 259.0735, found 259.0742.



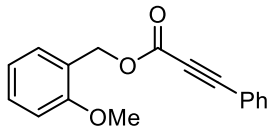
benzo[1,3]dioxol-5-ylmethyl 3-phenylpropiolate (SM-1-21)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 9.7, 4.7 Hz, 2H), 7.53 – 7.33 (m, 3H), 6.87 (dd, *J* = 39.2, 7.7 Hz, 3H), 6.14 – 5.83 (m, 2H), 5.17 (dd, *J* = 7.1, 3.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.08, 148.15, 148.06, 133.20, 130.88, 128.75, 123.06, 119.70, 109.59, 108.51, 101.44, 86.87, 80.65, 67.92.

HRMS calcd for $C_{17}H_{12}O_4Na$ [M+Na] 303.0633, found 303.0626.



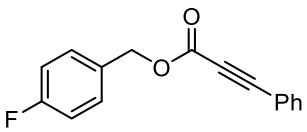
2-methoxybenzyl 3-phenylpropiolate (SM-1-25)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.52 (m, 2H), 7.37 (dq, *J* = 16.1, 7.9 Hz, 5H), 6.90 (s, 2H), 5.32 (d, *J* = 4.2 Hz, 2H), 3.86 (td, *J* = 5.4, 4.8, 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.89, 154.28, 133.18, 130.77, 130.49, 130.27, 128.72, 123.34, 120.64, 119.86, 110.69, 86.56, 80.87, 63.45, 55.64.

HRMS calcd for $C_{17}H_{14}O_3Na$ [M+Na] 289.0841, found 289.0840.



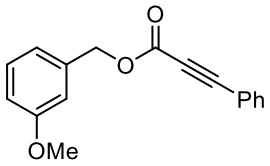
4-fluorobenzyl 3-phenylpropiolate (SM-1-26)

Yellow solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (t, *J* = 5.8 Hz, 2H), 7.40 (ddt, *J* = 19.9, 16.1, 7.0 Hz, 5H), 7.06 (tdq, *J* = 8.7, 5.8, 2.8 Hz, 2H), 5.30 – 5.13 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.06 (d, *J* = 247.1 Hz), 154.01, 133.22, 130.94 (d, *J* = 2.7 Hz), 130.86, 128.77, 119.62, 115.82 (d, *J* = 21.7 Hz), 87.08, 80.54, 67.15.

HRMS calcd for $C_{16}H_{11}FO_2Li$ [M+Li] 261.0903, found 261.0895.



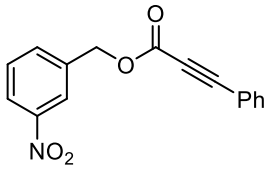
3-methoxybenzyl 3-phenylpropiolate (SM-1-22)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.1 Hz, 2H), 7.44 (d, *J* = 6.6 Hz, 1H), 7.37 (t, *J* = 7.0 Hz, 2H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.04 – 6.93 (m, 2H), 6.93 – 6.85 (m, 1H), 5.23 (d, *J* = 5.7 Hz, 2H), 3.82 (q, *J* = 2.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.96, 154.07, 136.54, 133.22, 130.90, 129.93, 128.76, 120.96, 119.69, 114.41, 114.11, 86.98, 80.63, 67.76, 55.48.

HRMS calcd for $C_{17}H_{14}O_3Na$ [M+Na] 289.0841, found 289.0840.



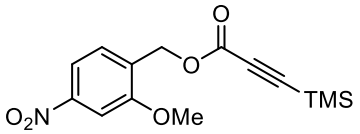
3-nitrobenzyl 3-phenylpropiolate (SM-1-23)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.27 (m, 1H), 8.22 (d, *J* = 7.1 Hz, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.58 (dt, *J* = 7.5, 4.5 Hz, 3H), 7.52 – 7.31 (m, 3H), 5.44 – 5.23 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.71, 148.59, 137.20, 134.41, 133.30, 131.15, 129.93, 128.83, 123.72, 123.42, 119.39, 87.87, 80.18, 66.26.

HRMS calcd for $C_{16}H_{11}NO_4Na$ [M+Na] 304.0586, found 304.0580.



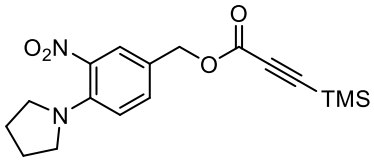
2-methoxy-4-nitrobenzyl 3-(trimethylsilyl)propiolate (SM-1-51)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 5.30 (s, 2H), 3.95 (s, 3H), 0.26 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.53, 152.75, 149.04, 130.81, 129.18, 115.92, 105.45, 95.55, 94.14, 62.14, 56.25, -0.71.

HRMS calcd for $C_{14}H_{17}NO_5Si$ [M+] 307.0876, found 307.0868.



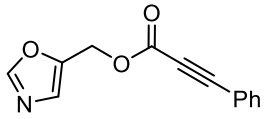
3-nitro-4-(pyrrolidin-1-yl)benzyl 3-(trimethylsilyl)propiolate (SM-1-48)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.2 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 2H), 3.28 – 3.14 (m, 4H), 2.03 – 1.94 (m, 4H), 0.23 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.65, 143.04, 136.51, 133.98, 127.90, 121.51, 116.33, 94.30, 75.38, 74.57, 67.10, 50.65, 25.86.

HRMS calcd for $C_{17}H_{22}N_2O_4SiLi$ [M+Li] 353.1509, found 353.1498.



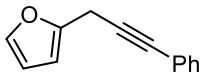
oxazol-5-ylmethyl 3-phenylpropiolate (SM-1-141)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.94 – 7.83 (m, 2H), 7.81 – 7.71 (m, 1H), 7.72 – 7.62 (m, 2H), 7.52 (s, 1H), 5.58 (s, 2H).

HRMS calcd for $C_{13}H_8NO_3$ [M-H] 226.0504, found 226.0511.

Characterization data for benzyl alkynes:



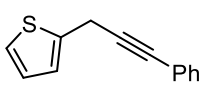
2-(3-phenylprop-2-yn-1-yl)furan (2.25)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.35 (d, *J* = 1.9 Hz, 1H), 7.31 – 7.27 (m, 3H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.26 (dq, *J* = 3.2, 1.1 Hz, 1H), 3.81 (d, *J* = 1.1 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.50, 141.94, 131.88, 128.41, 128.19, 123.48, 110.64, 106.42, 84.68, 82.02, 19.62.

HRMS Calcd for $C_{13}H_9O$ (M-H) – 181.0653, found 181.0638.

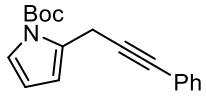


2-(3-phenylprop-2-yn-1-yl)thiophene (2.26)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 2H), 7.38 – 7.27 (m, 3H), 7.21 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.98 (dd, *J* = 5.1, 3.4 Hz, 1H), 4.01 (d, *J* = 1.1 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.77, 131.83, 128.42, 128.17, 127.04, 125.25, 124.29, 123.51, 86.86, 82.50, 20.84.



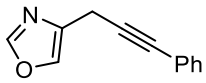
tert-butyl 2-(3-phenylprop-2-yn-1-yl)-1H-pyrrole-1-carboxylate (2.27)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.31 – 7.25 (m, 3H), 7.26 – 7.20 (m, 1H), 6.32 (dq, *J* = 3.0, 1.4 Hz, 1H), 6.12 (t, *J* = 3.3 Hz, 1H), 4.00 (d, *J* = 1.2 Hz, 2H), 1.59 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.54, 131.79, 130.24, 128.40, 127.98, 123.86, 121.75, 112.74, 110.27, 86.88, 84.09, 81.88, 28.18, 20.80.

HRMS Calcd for $C_{18}H_{19}NO_2$ (M+Na) 304.1313, found 304.1313.



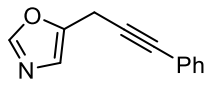
4-(3-phenylprop-2-yn-1-yl)oxazole (2.28)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 1.1 Hz, 1H), 7.61 (q, *J* = 1.3 Hz, 1H), 7.39 (ddd, *J* = 5.3, 2.7, 1.6 Hz, 2H), 7.30 – 7.17 (m, 3H), 3.69 (d, *J* = 1.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.41, 136.97, 135.71, 131.86, 128.44, 128.26, 123.35, 85.03, 82.21, 18.06.

HRMS Calcd for $C_{12}H_8NO$ (M+H) 184.0762, found 184.0774.



5-(3-phenylprop-2-yn-1-yl)oxazole (2.29)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 3.2 Hz, 1H), 7.39 (dt, *J* = 6.9, 3.2 Hz, 2H), 7.27 (td, *J* = 4.5, 4.0, 2.0 Hz, 2H), 7.21 (d, *J* = 3.2 Hz, 1H), 7.06 – 6.90 (m, 1H), 3.95 – 3.63 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.81, 147.96, 131.88, 128.50, 123.44, 122.98, 82.85, 82.59, 17.37.

HRMS Calcd for $C_{12}H_8NO$ (M+H) 184.0762, found 184.0756.

For the characterization data of substrates that are not included here, see ref.[2]

References

1. Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A., Decarboxylative Benzylations of Alkynes and Ketones. *J. Am. Chem. Soc.* **2010,** *132* (27), 9280-9282.

2. Torregrosa, R. R. P. Syntheses of Functionalized Benzylic Compounds: Development of Palladium-catalyzed Decarboxylative Benzylation Reactions Ph.D. Dissertation, The University of Kansas, KS, 2012.

Chapter 3

Palladium-catalyzed Stereospecific Decarboxylative Benzylation of Weakly-stabilized Nucleophiles

3.1 Introduction

The development of catalytic cross-coupling reactions to synthesize enantioenriched small molecules is an important and active area of research. In this regard, substantial progress has been made in coupling electrophilic partners with C(sp^2)–X bonds (e.g., aryl and vinyl halides and sulfonates).[1] In contrast, the asymmetric coupling of secondary alkyl and benzyl electrophiles bearing C(sp^3)–X bonds has met with more limited success.[2] A major issue with the latter is the increased steric demand of secondary alkyl and benzyl electrophiles, which slows down the oxidative addition step and increases the propensity for β-hydride elimination. Therefore, development of new asymmetric methods to overcome such limitations is a current need in synthetic chemistry.

The majority of the reported catalytic asymmetric coupling reactions are stereoconvergent reactions, which utilize chiral ligands to generate enantioenriched products from reactants that are racemic. Asymmetric cross-coupling reactions could also be carried out in a substrate controlled manner, which is known as a stereospecific synthesis. In a stereospecific coupling reaction, chiral information is transferred from a chiral nonracemic reactant to the product in the presence of an achiral catalyst (Figure 3.1). The stereospecificity of the reaction is denoted as a %cee value (conservation of enantiomeric excess), which is calculated by dividing the enantiomeric excess (ee) of the product by the ee of the starting material.

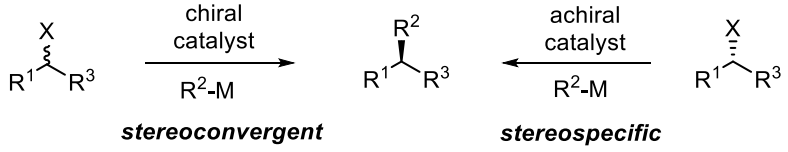


Figure 3.1

While catalyst controlled (stereoconvergent) reactions are often considered advantageous over substrate controlled (stereospecific) reactions in asymmetric synthesis, developing new synthetic methods for stereospecific coupling of benzyl electrophiles is highly desirable for several reasons: (I) benzyl halides are known to undergo S_N1 reactions with loss of stereochemistry,[3] (II) the preparation of enantioenriched starting material (benzyl alcohols) is often straightforward, (III) when the substituents about the chiral center are similar (e.g., 1,1-diarylalkyl derivatives), the facial selectivity of the chiral ligand is likely to be very poor in stereoconvergent reactions.

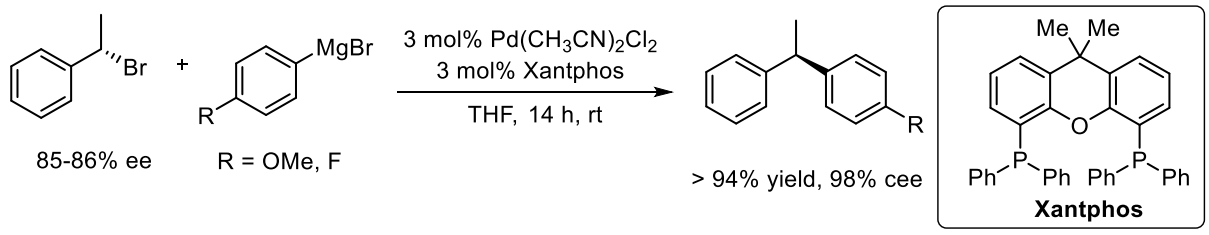
3.2 Palladium-catalyzed stereospecific cross-couplings of benzyl electrophiles

The first palladium-catalyzed stereospecific reaction of benzyl electrophiles was reported by Stille in the 1970s.[4] This work demonstrated that the oxidative addition of benzyl halides to Pd(0) occurs with inversion of stereochemistry (Chapter1.2, Scheme 1.3). Almost two decades later, Fiaud showed that the palladium-catalyzed benzylic substitution of enantioenriched benzyl carbonates with soft malonate nucleophiles occurs with overall retention of configuration and high stereochemical fidelity (Chapter 1.3, Scheme 1.11).

Apart from these initial reports, there are two other examples of Pd-catalyzed stereospecific cross-coupling reactions of benzylic electrophiles. In 2009, Adrio and Carretero reported a Pd-catalyzed Kumada-Corriu cross-coupling reaction using secondary benzylic bromides and aryl or vinyl Grignard reagents (Scheme 3.1).[5]

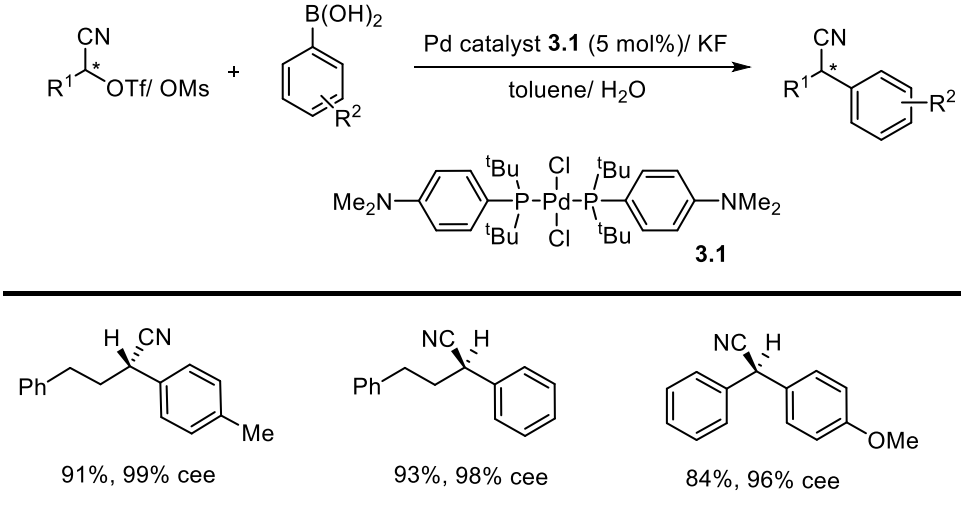
In their experiments, $Pd(CH_3CN)_2Cl_2$ and Xantphos in THF provided optimal results for the stereospecific coupling of (*S*)-1-bromoethylbenzene with *p*-methoxy and *p*-fluorophenyl magnesium bromide (Scheme 3.1). The coupling product was obtained in $\geq$ 98% cee with inversion

of configuration. Moreover, ligands with a larger bite angle, for example dppf (96°) and Xantphos (111°), prevented the formation of styrene via competitive β-hydride elimination.



Scheme 3.1

Another report details the stereospecific Suzuki cross-coupling of alkyl α-cyanohydrin triflates, as reported by Falck and co-workers in 2010 (Scheme 3.2).[6] Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) catalyst **3.1**, KF, and H_2O in toluene were employed to achieve the cross-coupling. In addition to enantiopure alkyl α-cyanohydrin triflates, benzylic mesylates also underwent highly stereospecific Suzuki coupling with aryl boronic acids, providing the coupling products in very good yields, with inversion of configuration.



Scheme 3.2

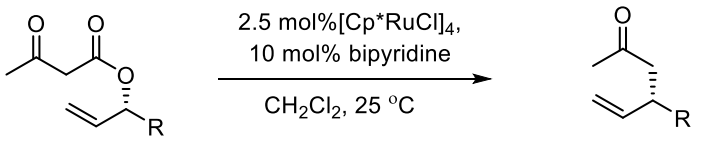
While there are no reports on catalytic stereospecific decarboxylative benzylation reactions reported in the literature, there are reported stereospecific decarboxylative coupling reactions that are limited to allylations, which proceed via chiral palladium-π-allyl intermediates.

3.3 Catalytic stereospecific decarboxylative allylations

Although there are a considerable number of reports on catalytic stereospecific allylic substitution reactions,[7] there are only a few reports on stereospecific decarboxylative allylation reactions.

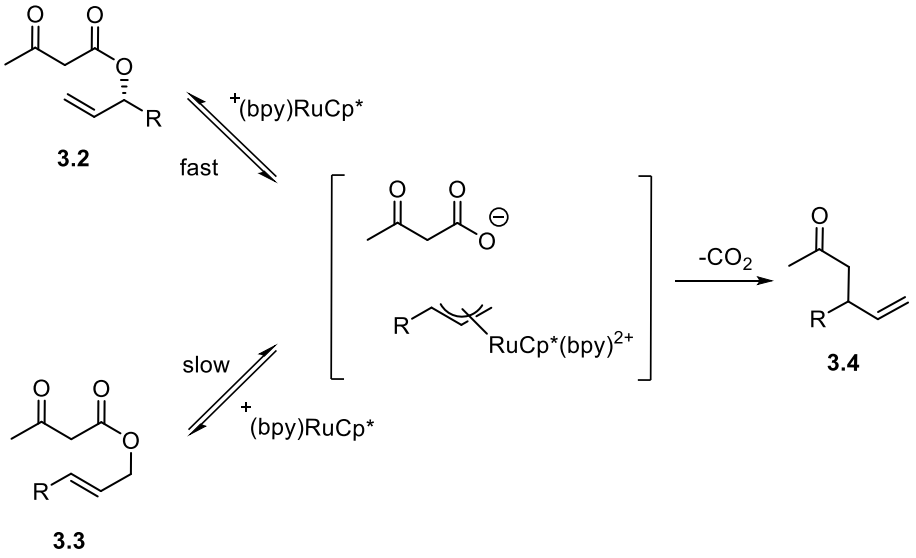
In 2005, Burger and Tunge disclosed a ruthenium-catalyzed stereospecific decarboxylative allylation of non-stabilized ketone enolates which proceeded via a decarboxylative Claisen (Carroll) rearrangement (Table 3.1).[8] Under optimized conditions for decarboxylative allylation, enantioenriched branched β-ketoesters provided enantioenriched homoallylic ketones with overall retention of configuration.

Table 3.1



entry	R	time (h)	cee %	yield %
1	Ph	1.5	83	86
2	*p*-C_6H_4OMe	0.25	93	83
3	*p*-C_6H_4Cl	0.5	94	56
4	*p*-C_6H_4Cl	4	86	70
5	*p*-$C_6H_4NO_2$	3	98	49

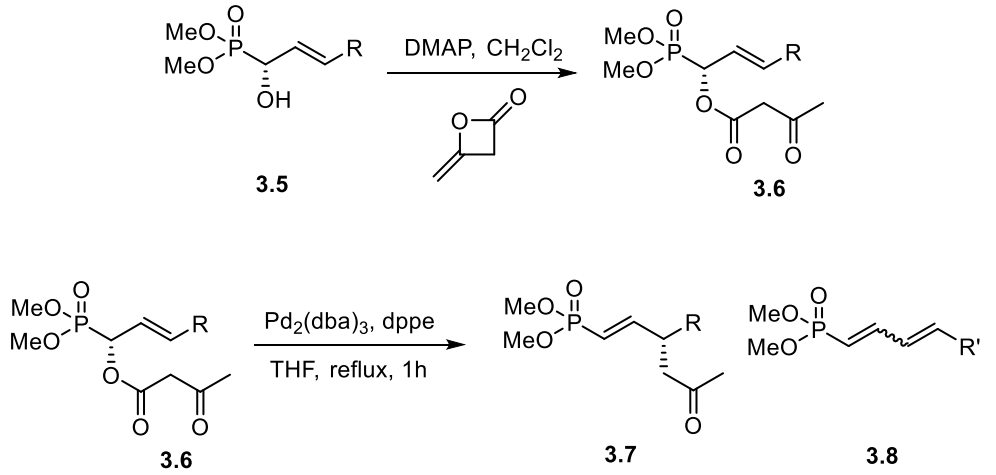
For substrates with a slower rate of conversion (for example Table 3.1, entry 3, 4 and 5), the stereospecificity of the reaction was dependent on the conversion to the product. Further investigation into this imperfect stereofidelity observed at longer reaction times revealed that, over the course of the reaction, the enantioenriched branched β-ketoester (**3.2**) was being converted to the racemic isomeric linear β-ketoester (**3.3**). Decarboxylative allylation of **3.3** then lead to racemic **3.4**, lowering the cee (Scheme 3.3). This observation ruled out the contribution from a possible π–σ–π isomerization of Ru-allyl intermediate for the lowered cee.



Scheme 3.3

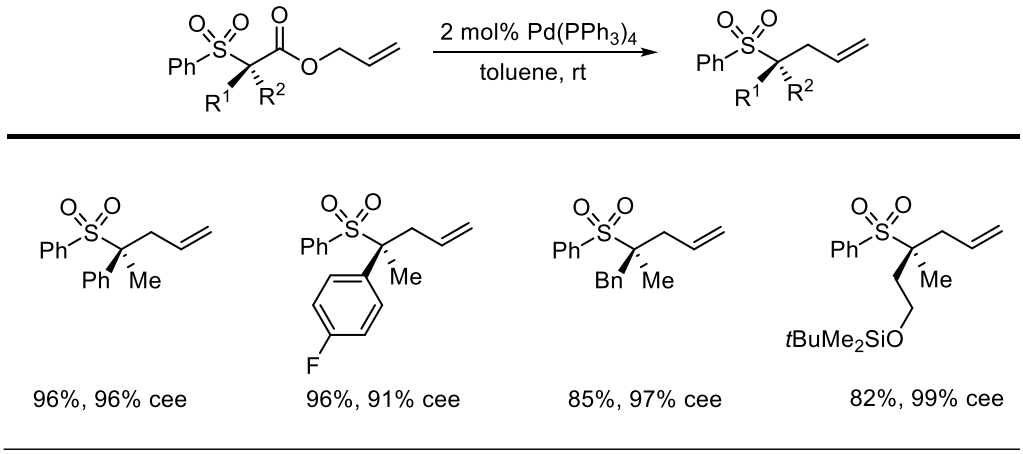
A similar Pd-catalyzed decarboxylative rearrangement of β-ketoesters was also reported by Yan and Spilling in 2008 (Table 3.2).[9] In the presence of $Pd_2(dba)_3$ and dppe in refluxing THF, enantioenriched phosphono allylic acetoacetates (**3.6**) underwent highly stereospecific decarboxylative rearrangement to provide non racemic vinyl phosphonates (**3.7**) with overall retention. However, the formation of diene **3.8** via β-hydride elimination was unavoidable for substrates with β-hydrogens.

Table 3.2



entry	R	ee % **3.5**	yield % (ee %) **3.7**	yield % (ee %) **3.8**
1	*n*-C_5H_{11}	71	56 (71)	27
2	CH_3	70	71 (70)	2
3	$CH_2CH(CH_3)_2$	(±)	35 (±)	31

In addition to the stereospecific decarboxylative allylation of ketone enolates, Tunge and co-workers further disclosed a highly stereospecific decarboxylative allylation of α-sulfonyl anions, to generate homoallylic sulfones with overall retention (Scheme 3.4). Remarkably, allylation of sulfones occurred in high stereofidelity even at high temperatures (100 °C). Therefore, DFT calculations were performed to calculate the energies associated with the possible modes of racemization of the α-sulfonyl anion. These calculations showed that the barrier for inversion of the α-sulfonyl anion is <2 kcal/mol (Figure 3.2). While DFT data ruled out the slow inversion of the anion as a possible mode for racemization, it was suggested that the high stereospecificity results from a more stable conformer of the anion (**3.9**) which has the lone pair oriented antiperiplanar to the S–Ph bond and slow rotation about the S–C bond (9.9 kcal/mol).



Scheme 3.4

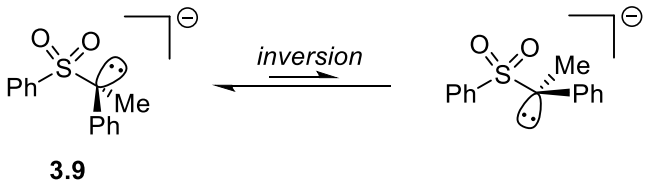
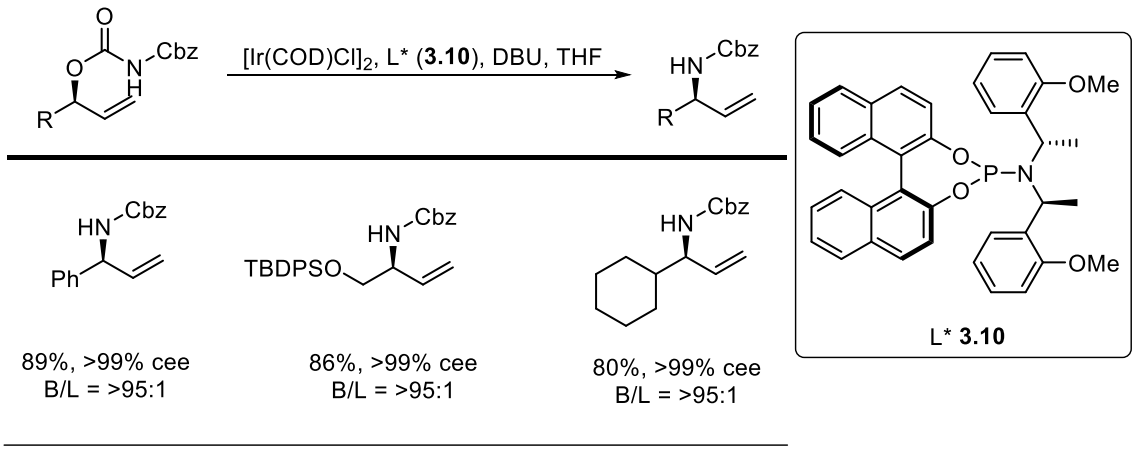


Figure 3.2

In 2007, Singh and Han reported an Ir-catalyzed stereospecific decarboxylative allylic amidation (Scheme 3.5) to overcome the limitations of their enantioselective synthesis,[10] which was mostly limited to sterically small allyl substituents. Moreover, competing β-hydride elimination was problematic. In the reported stereospecific reaction enantioenriched branched Cbz-protected carbamates underwent decarboxylative allylation to generate enantioenriched allylic carbamates with overall retention, via a double inversion mechanism involving an Ir-π-allyl intermediate. Since the decarboxylative coupling occurred with high stereochemical fidelity, the epimerization via π-σ-π isomerization was slow. The reaction proceeded in the presence of $[Ir(cod)Cl]_2$, a chiral phosphoramidite ligand **3.10** and DBU in THF at room temperature.

However, the chiral ligand had no effect on the stereochemistry of the reaction, and it was simply used due to the ineffectiveness of other achiral ligands.



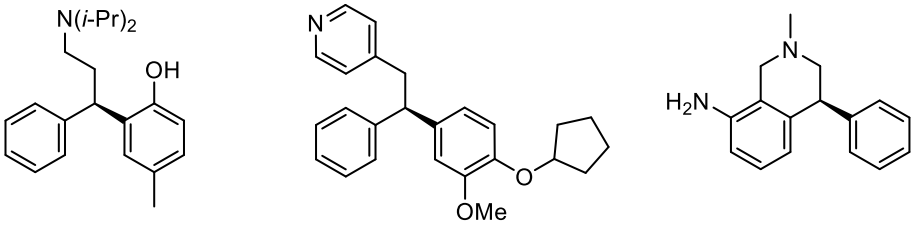
Scheme 3.5

3.4 Palladium-catalyzed stereospecific decarboxylative benzylation reactions with weakly-stabilized nucleophiles

In light of the reported metal-catalyzed stereospecific decarboxylative allylic cross-coupling reactions, we sought to implement a stereospecific decarboxylative benzylic cross-coupling reaction with less-stabilized nucleophiles (pK_a >20), under palladium-catalyzed conditions. Given the fact that the chiral palladium-π-benzyl intermediates do not epimerize rapidly during reaction with stabilized nucleophiles,[11] our pursuit of a highly stereospecific coupling of benzyl electrophiles with less stabilized nucleophiles seemed reasonable.

We were specifically interested in benzylic electrophiles with the 1,1-diarylalkyl motif, due to their prevalence in pharmaceuticals, such as tolterodine **3.11**,[12] CDP-840 **3.12**,[13] and nomifensine **3.13**.[12c, 14] Moreover, the 1,1-diarylalkyl structural unit could also be found in compounds that show biological activity as antimuscarinics,[15] antidepressants,[16] and endothelin antagonists.[17]

Furthermore, the need of developing practical asymmetric methods for the synthesis of optically pure compounds with 1,1-diarylalkyl subunits was also highlighted in a recent publication from the Merck Frosst center for therapeutic research.[18]



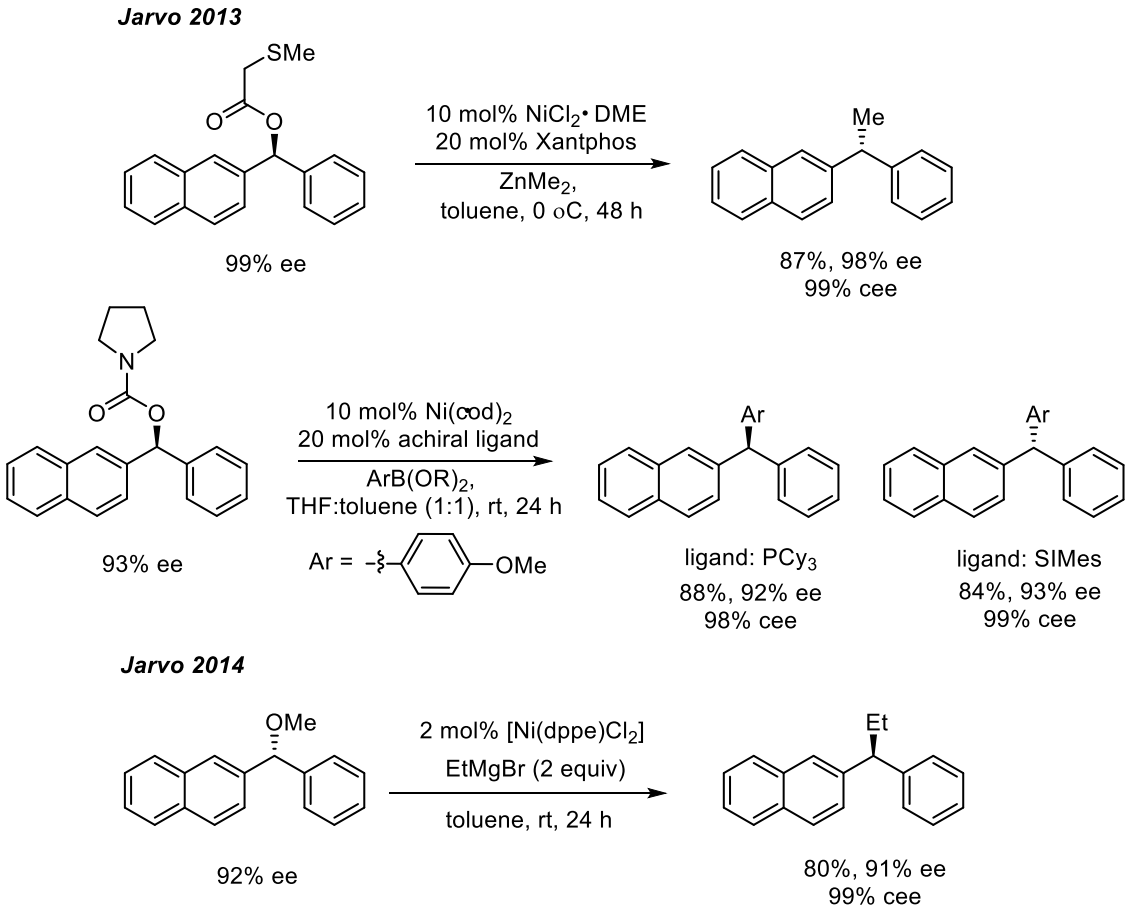
3.11 **3.12** **3.13**

A few of the reported synthetic methods for the induction of chirality in 1,1-diarylalkyl subunits include asymmetric epoxidations,[19] asymmetric conjugate addition of organometallic reagents to cinnamates,[20] aryl cuprate additions to enantioenriched cyclopropane dicarboxylates,[21] catalytic asymmetric C–H insertion of rhodium carbenoids into cyclohexadienes,[12c] and asymmetric reductions.[22]

Additionally, the Jarvo (Scheme 3.6) and Watson groups have implemented nickel-catalyzed stereospecific cross-coupling reactions of 1,1-diarylalkyl electrophiles to generate enantioenriched molecules with a tertiary stereogenic center.[23] Since benzyl halides lose stereochemical information in the oxidative addition step of nickel catalyzed processes,[24] benzyl ethers and benzyl esters were employed for the successful transfer of stereochemical information from reactants to the products via a chiral nickel-π-benzyl intermediate.[23a-c, 23e, 23f] Moreover, an unusual stereospecific cross-coupling reaction of benzylic carbamates with arylboronic esters was also developed, in which the stereochemical outcome of the product depends on the achiral ligand used.[23c] In the presence of PCy_3, reaction occurs with retention, while SIMes delivers the product with inversion. However, the exact mechanisms that operate in these achiral ligand-dependent

stereospecific pathways is currently unknown.[23e, 23g] Furthermore, all of these stereospecific coupling reactions require the use of preformed organometallics.

Similarly, synthesis of enantioenriched 1,1-diaryl substrates would benefit greatly from stereospecific decarboxylative coupling, because the enantioenriched carboxylic acid derivatives could be easily synthesized from the respective enantiopure diarylmethanols, which are readily available via asymmetric alkylation,[25] and asymmetric hydrogenation methods.[26]



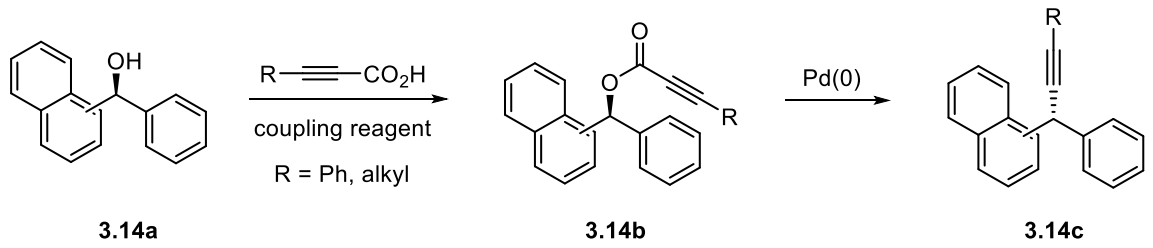
Scheme 3.6

Based on previous work on palladium-catalyzed decarboxylative benzylation of alkynes,[27] we thought to implement a highly stereospecific palladium-catalyzed decarboxylative benzylation strategy to synthesize enantiopure 1,1-diarylethynyl methanes. Despite the significant

advancements made in transition metal-catalyzed asymmetric cross-coupling reactions, the asymmetric alkynylation of secondary benzyl electrophiles is scarcely reported in the literature.[28] Moreover, there is not any direct approach reported for the synthesis of enantioenriched 1,1-diarylethynyl methanes, which can serve as valuable precursors for the synthesis of enantioenriched 1,1-diarylmethanes.

3.4.1 Development of stereospecific decarboxylative benzylation of alkynes

We envisioned the synthesis of enantioenriched 1,1-diarylethynyl methanes **3.14c** via the palladium-catalyzed decarboxylative coupling of enantioenriched benzyl esters **3.14b**. These benzyl esters could be synthesized from the respective enantiopure diarylmethanols **3.14a** (Scheme 3.7).

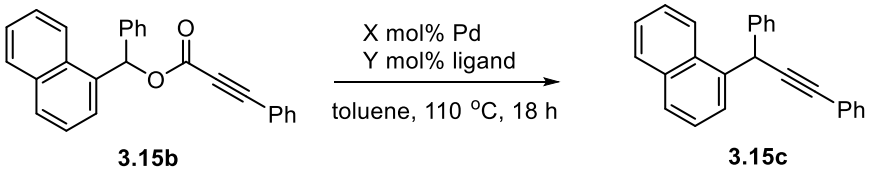


3.14a **3.14b** **3.14c**

Scheme 3.7

To begin, racemic benzylic ester **3.15b** was synthesized from the respective racemic diarylmethanol via standard DCC/DMAP coupling.[27] Then a variety of catalyst/ligand combinations were evaluated (Table 3.3) for the decarboxylative coupling of **3.15b**, with the goal of developing the stereospecific reaction. As it was previously shown,[27] 10 mol% $Pd(PPh_3)_4$ at 110 °C in toluene provided the highest conversion to **3.15c** (entry 19). No cross-coupled product was observed in the absence of $Pd(PPh_3)_4$.

Table 3.3



3.15b **3.15c**

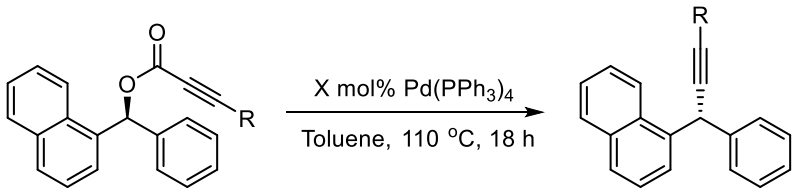
entry	X	Pd	Y	ligand	conversion to **3.15c** (%)[a]
1	5	Pd_2dba_3	20	XPhos	0
2	5	Pd_2dba_3	10	Xantphos	0
3	5	Pd_2dba_3	10	dppe	0
4	5	Pd_2dba_3	20	PPh_3	6
5	5	Pd_2dba_3	20	$P(1\text{-Np})_3$	0
6	5	Pd_2dba_3	20	PCy_3	0
7	10	CpPd(allyl)	11	dppe	0
8	10	CpPd(allyl)	11	Rac-BINAP	0
9	10	CpPd(allyl)	11	*S*-DIBM SEGPHOS	0
10	10	CpPd(allyl)	20	$P(1\text{-Np})_3$	0
11	10	CpPd(allyl)	20	PBu_3	0
12	10	CpPd(allyl)	20	PCy_2bp	0
13	10	CpPd(allyl)	20	$P(t\text{-}Bu_3)$	0
14	10	CpPd(allyl)	20	PCy_3	0
15	10	CpPd(allyl)	11	dppf	0
16	10	CpPd(allyl)	11	Xantphos	0
17	20	CuI	—	none	0
18	10	$[Pd(allyl)COD]BF_4$	20	$P(1\text{-Np})_3$	0
19	10	$Pd(PPh_3)_4$	—	none	82
20		—		—	0

[a] Determined by ^1H NMR spectroscopy.

Next, we examined the stereospecificity of this cross-coupling reaction. Highly enantiopure **(*S*)-3.15b** was synthesized from the corresponding enantiopure alcohol.[29] Gratifyingly, the decarboxylative benzylation of **(*S*)-3.15b** occurred with high stereochemical fidelity to provide the benzyl alkyne **(*R*)-3.15c** with a 94% cee (Table 3.4, entry 1) under optimized reaction conditions (Table 3.3, entry 19). Remarkably, increasing the catalyst loading to 15 mol%, and 20 mol% did not show a significant effect on the yield or the stereospecificity of the reaction (Table 3.4, entry 2 and 3). This is in contrast to previous reports, where a higher catalyst loading lowered the

enantiospecificity of the reaction due to racemization of the chiral palladium-π-benzyl intermediate, presumably via the attack of a second palladium species on the palladium-π-benzyl intermediate (Figure 3.3).[11, 30]

Table 3.4



(*S*)-3.15b (*R*)-3.15c

entry	catalyst loading (X mol %)	(*S*)-3.15b ee %[a]	(*R*)-3.15c ee %[a]	yield %[b]	cee %
1	10	94	88	85	94
2	15	94	89	87	95
3	20	94	84	90	89

[a]Determined by chiral HPLC analysis, [b]Yield of isolated product **3.15** from column chromatography

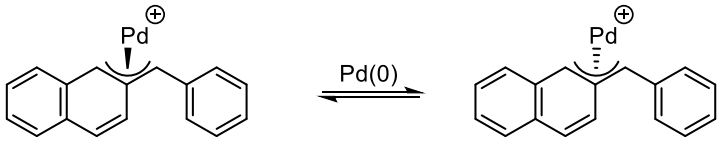
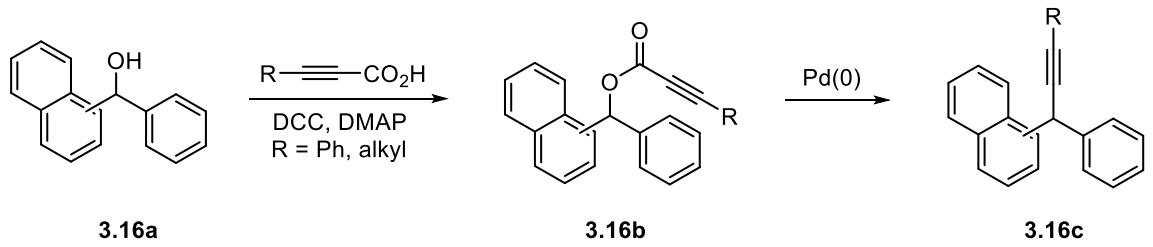


Figure 3.3

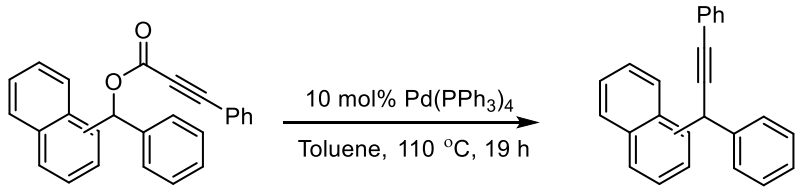
Next, we synthesized a range of racemic benzylic ester derivatives **3.16b**, via the DCC/ DMAP coupling of respective racemic diarylmethanols **3.16a**, with propiolic acid substrates (Scheme 3.8).[27] Racemic diarylmethanols were prepared by methods reported in literature.[23c, 31] Under optimized reaction conditions the racemic benzyl esters underwent decarboxylative benzylation to provide benzyl alkynes **3.16c**.



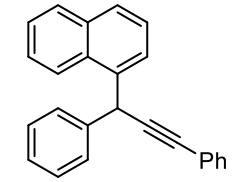
3.16a **3.16b** **3.16c**

Scheme 3.8

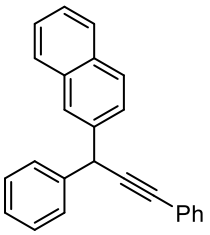
The substrate scope for the racemic decarboxylative benzylation of alkynes is shown in scheme 3.9). In general, when electron donating substituents are present on the naphthyl or phenyl ring, benzyl alkynes are formed in very good yields (**3.18c - 3.22c**). This is probably due to the stabilization of the cationic palladium-π-benzyl intermediate by electron rich substrates. With the *ortho*-methoxy substrate (**3.23c**) the yield was lowered due to steric hindrance. The *para*-fluoro (**3.24b**) and *para*-chloro (**3.28b**) substituted phenyl propiolates also provided good yields. While inductively electron withdrawing *meta*-methoxy phenyl propiolate provided the respective benzyl alkyne **3.27c** in a very good yield, *meta*-chloro (**3.29c**), *meta*-alkyl (**3.30c**) and di-substituted benzyl alkyne (**3.25c** and **3.31c**) were formed in moderate yields. However, the phenyl propiolate substrates **3.32b - 3.34b** did not react under optimized reaction conditions, and we were able to isolate the unreacted benzyl ester to account for the mass-balance (Scheme 3.10). We think that the steric hindrance caused by the *ortho*-methyl group of **3.32b**, prevented the palladium-π-benzyl formation on the extended arene. Substrate **3.34b** was also unreactive towards the optimized conditions, presumably due to the presence of a *meta*-bromo substituent. However, the change of *meta*-bromo to a *meta*-chloro provided the benzyl alkyne **3.22c** in very good yield.



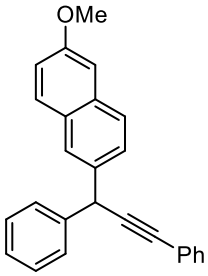
3.15b - 3.32b **3.15c - 3.32c**



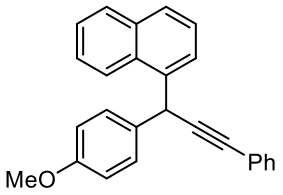
3.15c, 80%



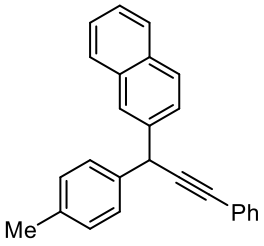
3.17c, 79%



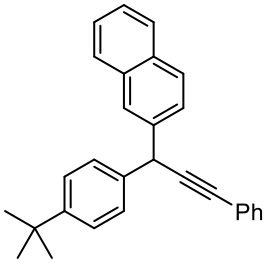
3.18c, 81%



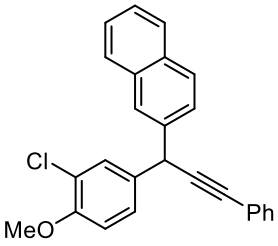
3.19c, 84%



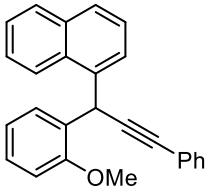
3.20c, 88%



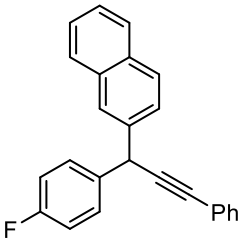
3.21c, 93%



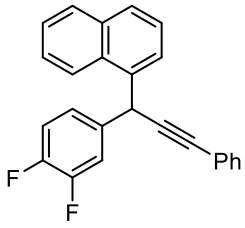
3.22c, 89%



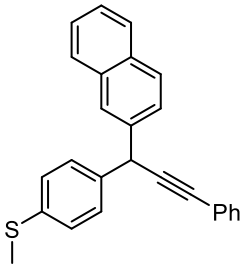
3.23c, 51%



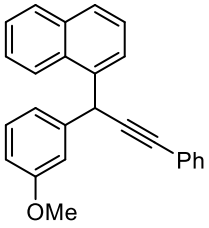
3.24c, 72%



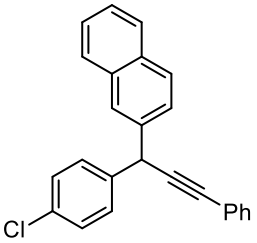
3.25c, 62%



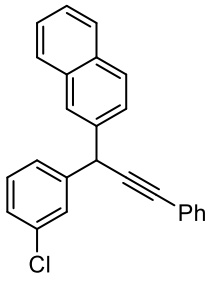
3.26c, 60%



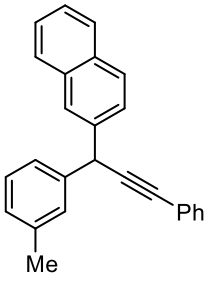
3.27c, 82%



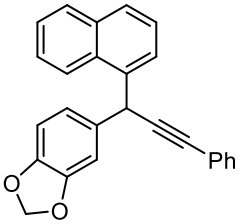
3.28c, 79%



3.29c, 59%

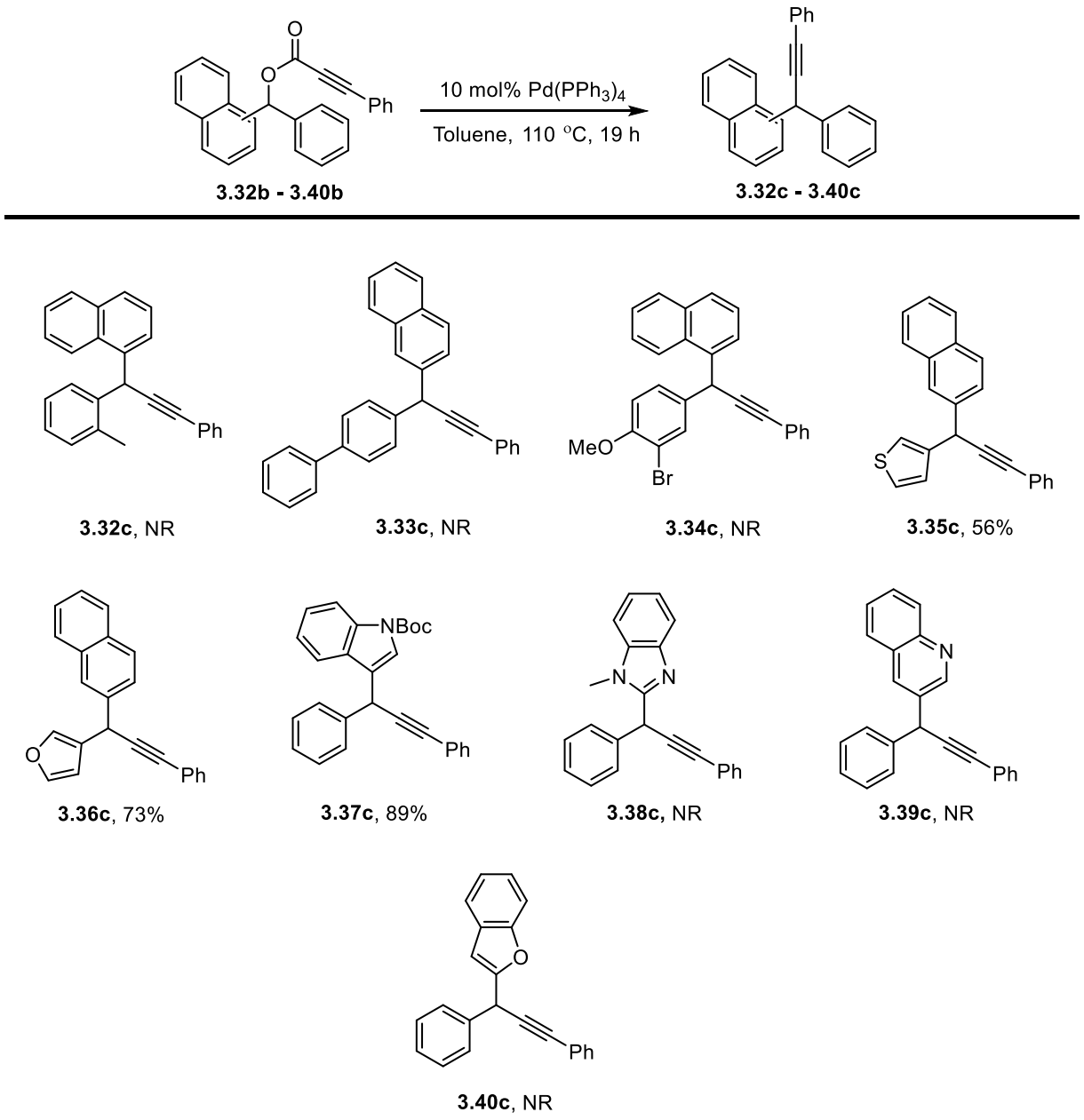


3.30c, 51%



3.31c, 52%

Scheme 3.9

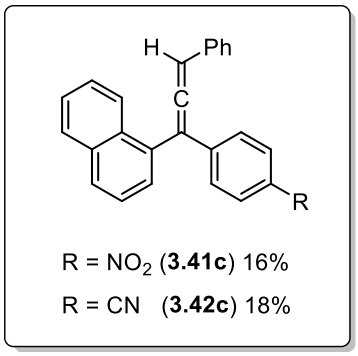


Scheme 3.10

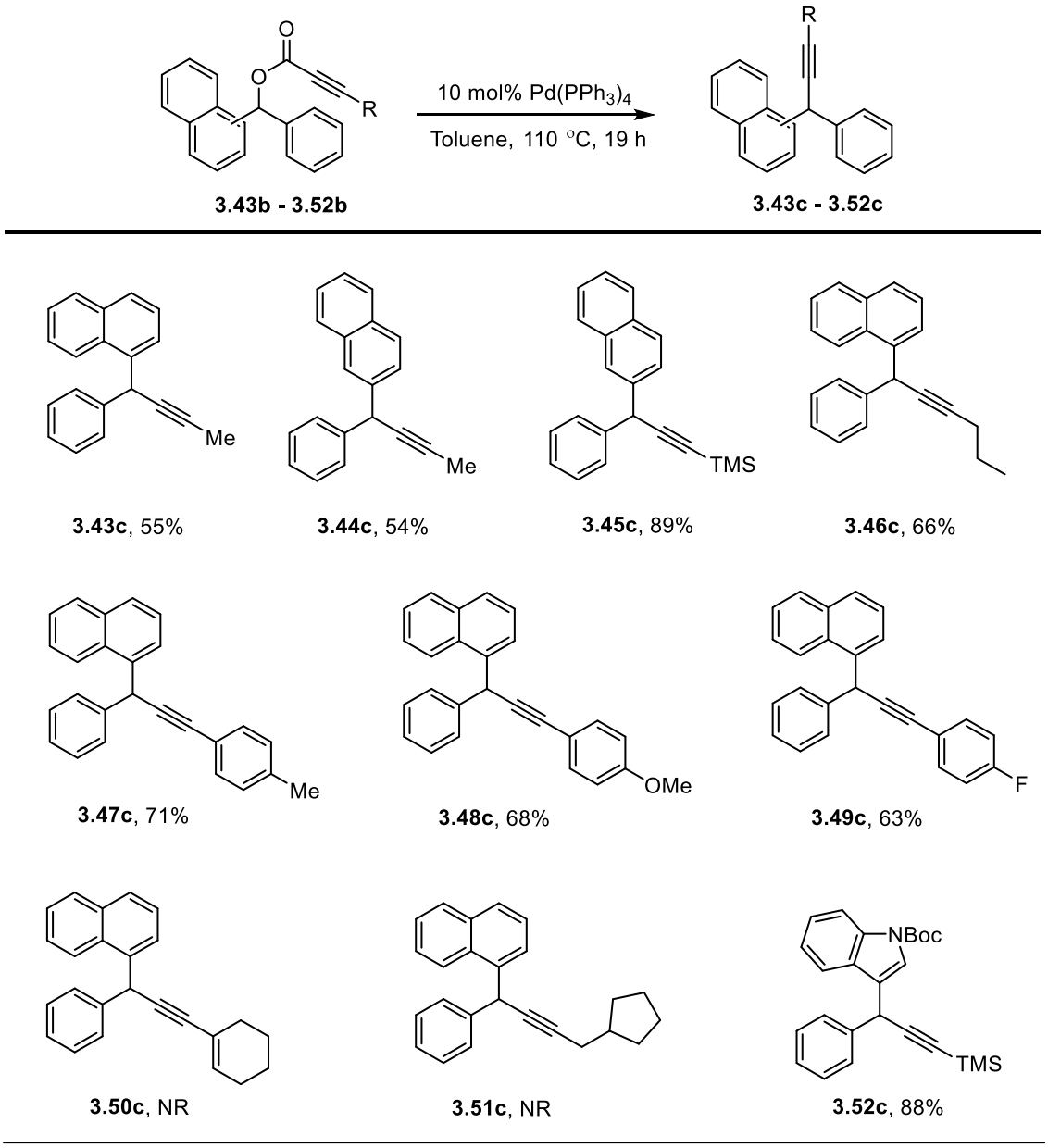
Palladium-catalyzed decarboxylative coupling is also applicable to the synthesis of 1,1-diarylethynyl methanes with heteroaromatic aryl groups (Scheme 3.10). Thiophene (**3.35c**), furan (**3.36c**) and indole (**3.37c**) moieties were well-tolerated and provided the cross-coupled alkynes in

good yields. However, among the heteroaromatic substrates with extended-π conjugation, indole was the only heteroaromatic moiety that was able to form the cross-coupled product **3.37c** in very good yield in the absence of a 1- or 2-naphthyl moiety, presumably via the formation of a palladium-π-indolyl intermediate. Phenyl propiolate esters with *N*-methylbenzimidazole (**3.38b**), 3-quinoline (**3.39b**), and 2-benzofuran (**3.40b**) did not provide the expected alkyne product.

Substrates with highly electron withdrawing substituents, for example, *para*-nitro and *para*-cyano substituted phenyl propiolates, provided the allene products (**3.41c** and **3.42c**) in a very low yield via the isomerization of the alkyne, and the unreacted ester was isolated to account for the mass balance.



Next we looked at the substrate scope for the propiolic acid coupling partner (Scheme 3.11). It was gratifying to find that, in addition to phenyl propiolates, alkyl (**3.43c**, **3.44c**, and **3.46c**), trimethylsilyl (**3.45c** and **3.52c**) and substituted phenyl propiolates (**3.47c - 3.49c**) also underwent decarboxylative coupling to provide the products in moderate to good yields. While trimethylsilyl protected alkynes (**3.45c** and **3.52c)** always resulted in a high yield, methyl alkynes (**3.43c** and **3.44c**) were formed in moderate yield. However, cyclohexenyl alkyne **3.50c** and cyclopentylmethyl alkyne **3.51c**, could not be synthesized under optimized reaction conditions.



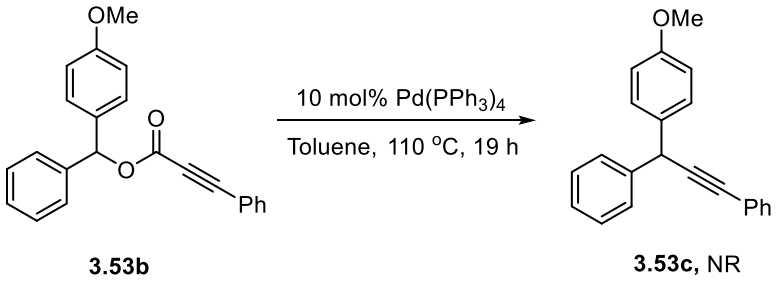
3.43c, 55% **3.44c**, 54% **3.45c**, 89% **3.46c**, 66%

3.47c, 71% **3.48c**, 68% **3.49c**, 63%

3.50c, NR **3.51c**, NR **3.52c**, 88%

Scheme 3.11

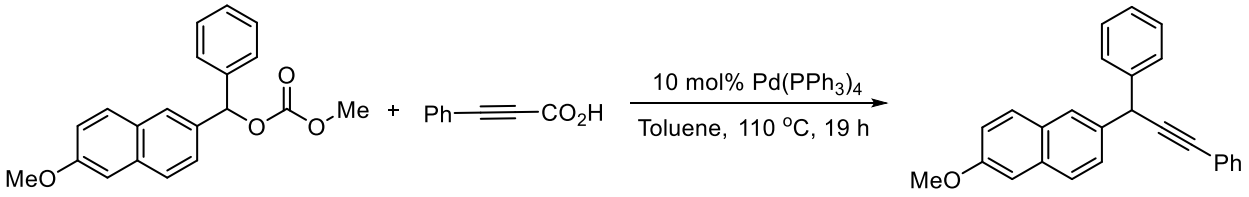
Unfortunately, our efforts to extend the electrophile scope to "simple" benzyl esters, which do not have extended π-systems was unsuccessful (Scheme 3.12). It was disappointing to isolate the unreacted benzyl ester **3.53b**, without any product formation, under standard reaction conditions.



3.53b **3.53c,** NR

Scheme 3.12

Additionally, we tried to develop a one-pot reaction for the coupling of benzyl electrophiles with alkynes, using benzyl methyl carbonate **3.18d** and phenylpropiolic acid (Scheme 3.13). Unfortunately, all attempts were unsuccessful, and we only isolated the unreacted **3.18d**.

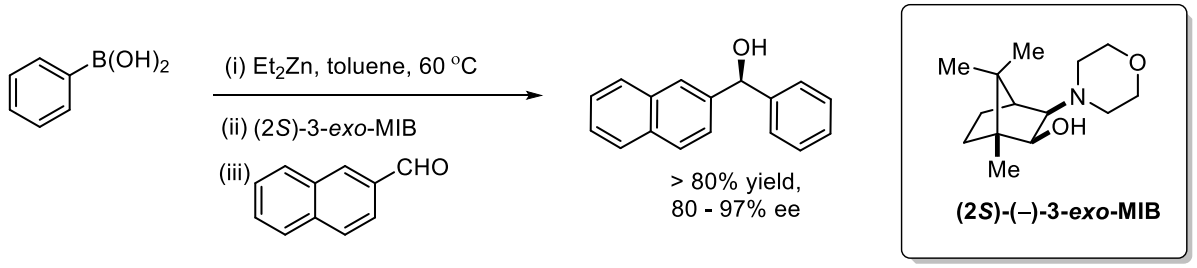


3.18d **3.18c**, NR

Scheme 3.13

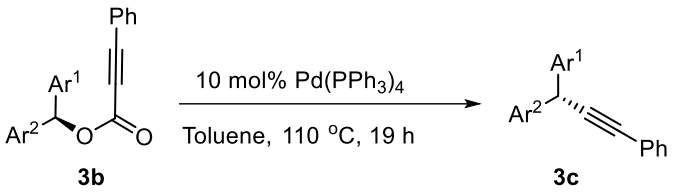
Next, enantioenriched benzylic ester derivatives (**3.14b)** were synthesized via the DCC/ DMAP or PyBop coupling of the respective enantioenriched diaryl alcohol with the propiolic acid substrate (Scheme 3.7). Highly enantioenriched diaryl alcohols could be obtained by slightly modifying the procedure reported by Braga. In the enantioenriched diarylmethanol synthesis, we used a more bulky chiral amino alcohol (2*S*)-(–)-3-*exo*-MIB as the chiral ligand, instead of the originally reported chiral ligand in Braga's report.[32] This procedure generally provided the enantioenriched diarylmethanols with 80-97% ee except for some [**(*S*)-3.23a** and **(*R*)-3.31a**] where a lower ee was obtained (Scheme 3.14). An additional advantage of this method is that either

enantiomer of the diarylmethanol could be obtained via the appropriate selection of the aryl boronic acid and the aryl aldehyde.



Scheme 3.14

We then investigated the scope of the stereospecific decarboxylative benzylation reaction (Table 3.5). A variety of substituted benzo-fused propiolates underwent stereospecific decarboxylative benzylation with excellent enantiospecificity, providing moderate to good yields. Reactants of substrates bearing substituents at the *para*-position with a halogen **(*R*)-3.24c, (S)-3.28c** or alkyl group **(*R*)-3.20c, (*R*)-3.21c** provided the cross-coupled product in high yield and high enantiospecificity. Interestingly, we could access both enantiomers of **(*R*)-3.24c** and **(S)-3.28c** in high ee, via the appropriate selection of aryl aldehyde and aryl boronic acid. Inductively electron donating methyl **(*R*)-3.30c** and inductively electron withdrawing -OMe substituents at the *meta*-position **(*R*)-3.27c** also provided satisfactory results. However, good electron donors in the *ortho* or *para*-position led to partial racemization of the benzylic ester derivative [**(*S*)-3.23b**, **(*S*)-3.26b**, **(*R*)-3.31b**, **(*R*)-3.22b]**. Different coupling reagents (DCC-DMAP, PyBop and HOBT) were used to couple benzyl alcohols with propiolic acids in order to optimize the ee in the esterification reactions. However, the partial racemization of highly electron rich benzyl esters was unavoidable.



3b **3c**

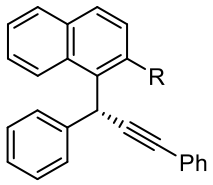
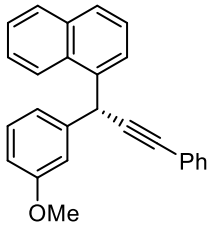
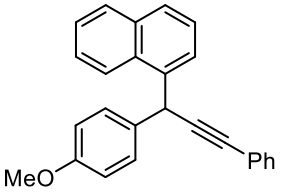
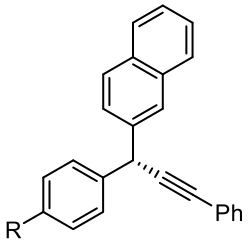
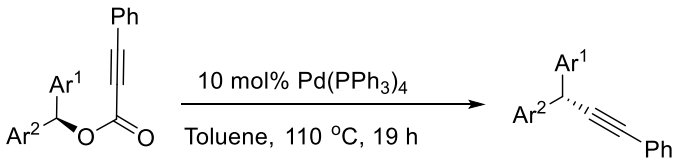
entry	reactant ee(%) [a]	product		yield (%) [b]	ee (%) [a]	cee (%)
						
1	94	R = H	**(*R*)-3.15c**	85	88	94
2	69	R = OMe	**(*R*)-3.23c**	31	64	93
3	97		**(*R*)-3.27c**	81	96	99
4[c]	-		**3.19c**	87	2	-
						
5	94	R = F	**(*R*)-3.24c**	83	92	98
6	>85	R = Me	**(*R*)-3.20c**	77	95	>99
7	62	R = SMe	**(*R*)-3.26c**	68	43	69
8	94	R = ^{t}Bu	**(*R*)-3.21c**	92	89	95

Table 3.5



3b **3c**

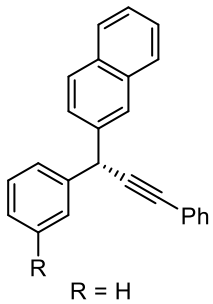
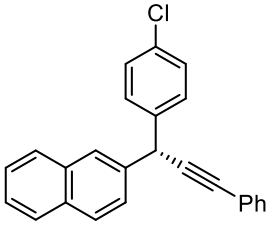
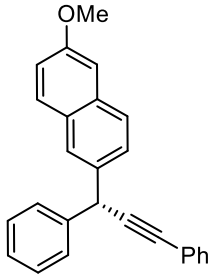
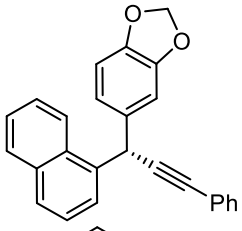
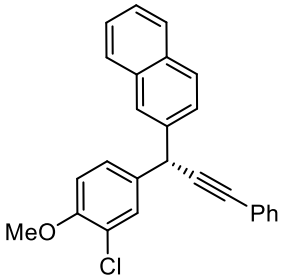
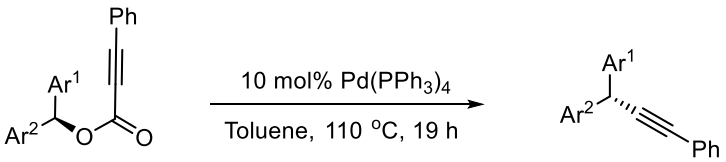
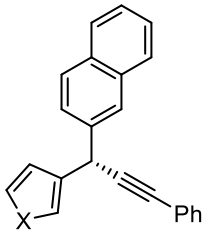
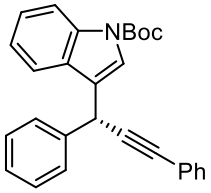
entry	reactant ee(%) [a]	product		yield (%) [b]	ee (%) [a]	cee (%)
9	92		R = H **(*R*)-3.17c**	84	89	97
10	94		R = Me **(*R*)-3.30c**	71	91	97
11	91		**(*S*)-3.28c**	73	93	>99
12	81		**(*R*)-3.18c**	73	79	98
13	-		**(*S*)-3.31c**	53	27	-
14	42		**(*S*)-3.22c**	81	63	>99

Table 3.5



3b **3c**

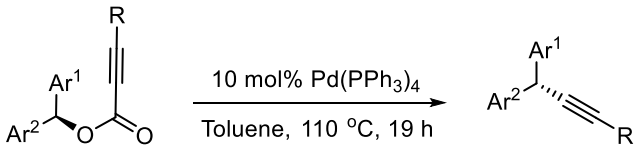
entry	reactant ee(%) [a]	product	yield (%) [b]	ee (%) [a]	cee (%)
15	72	 X = S	**(*S*)-3.35c**	69	64	89
16	75	X = O	**(*S*)-3.36c**	77	64	85
17	87		**(*R*)-3.37c**	92	60[e]	69

[a] Determined by chiral HPLC analysis. [b] Yield of isolated product after column chromatography on silica gel. All products were stored cold upon isolation. [c] The %ee of **3.19b** and **(*R*)-3.31b** is unknown because these did not separate by HPLC using Chiralcel OD, OD-H and Chiralpak AD, AD-H and AS-H chiral columns. [e] The Boc group was removed prior to HPLC analysis.

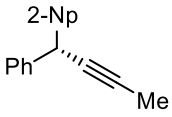
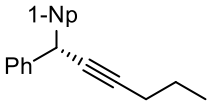
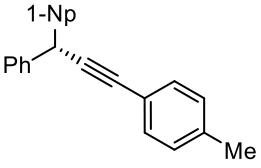
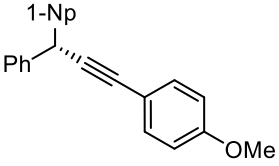
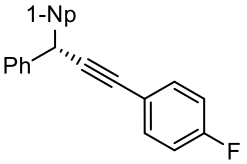
Table 3.5

The para-methoxy substrate **3.19c** was obtained as a nearly racemic mixture. Since the benzyl ester **3.19b** was not separable by HPLC (using Chiralcel OD, OD-H and Chiralpak AD, AD-H and AS-H chiral columns), we do not know whether the benzyl ester was racemized or whether the racemization occurred during the reaction.

Interestingly, heteroaromatic phenyl propiolates [**(*S*)-3.35c, (*S*)-3.36c,** and **(*R*)-3.37c**] also underwent stereospecific decarboxylative benzylation with high stereochemical fidelity.



3b **3c**

entry	reactant ee(%) [a]	product		yield (%) [b]	ee (%) [a]	cee (%)
1	92		**(*R*)-3.44c**	43[c]	87	95
2	93		**(*R*)-3.46c**	53	81	87
3	91		**(*R*)-3.47c**	62	85	93
4	86		**(*R*)-3.48c**	87	77	90
5	91		**(*R*)-3.49c**	59	87	96

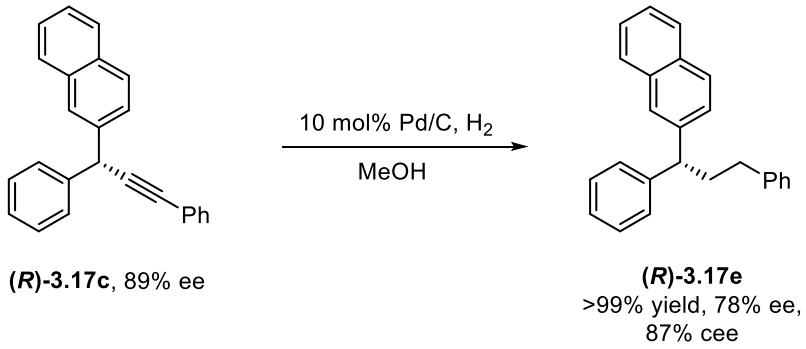
[a] Determined by chiral HPLC analysis. [b] Yield of isolated product after column chromatography on silica gel. All products were stored cold upon isolation. [c] Isolated yield after 16 h.

Table 3.6

Next, the scope of the acetylide coupling partner was examined (Table 3.6). In addition to phenyl propiolates, alkyl [**(*R*)-3.44c, (*R*)-3.46c**] and substituted phenyl propiolates [**(*R*)-3.47c - (*R*)-3.49c**] also underwent decarboxylative benzylation with high stereospecificity. The synthesis and purification of trimethylsilyl protected propiolates (**3.45b** and **3.52b**) were not problematic

initially. However, racemic or enantioenriched trimethylsilyl protected propiolates could not be synthesized with reproducibility due to its instability on the silica column, even under slightly basic conditions. This could be due to differences in the silica that was used as there was a significant time gap between syntheses of the trimethylsilyl protected propiolates. Therefore, the stereospecific cross-coupling could not be carried out to yield enantioenriched trimethylsilyl protected benzyl alkynes.

To show the potential to make other tertiary diarylmethane compounds, we briefly looked at the stereospecificity of the catalytic hydrogenation of benzyl alkyne **(*R*)-3.17c**, in the presence of 10 mol% Pd/C and H_2 (Scheme 3.15). We were pleased to obtain the reduced product **(*R*)-3.17e** in 78% ee, and 87% cee.

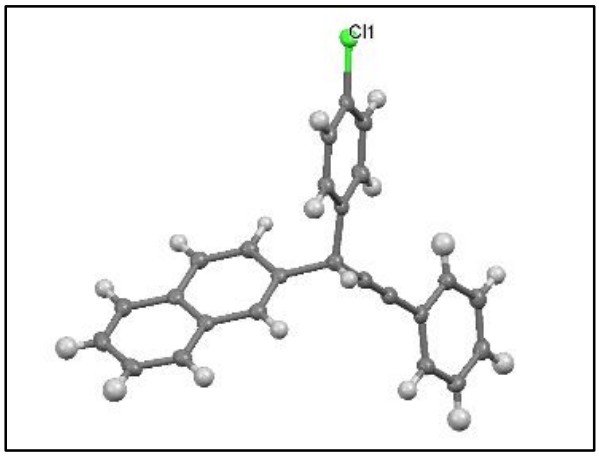


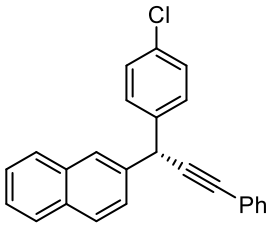
(*R*)-3.17c, 89% ee

(*R*)-3.17e
>99% yield, 78% ee,
87% cee

Scheme 3.15

Next, we turned our interest towards the mechanism of the stereospecific decarboxylative benzylation of alkynes. Particularly, we were curious to know whether the benzyl-alkyne coupling proceeds with retention or inversion of configuration. We crystallized the *para*-chloro benzyl alkyne **(*S*)-3.28c**, and obtained an x-ray crystal structure (Figure 3.4). The absolute configuration of the product **(*S*)-3.28c** was determined to be (*S*) by x-ray crystallographic analysis.

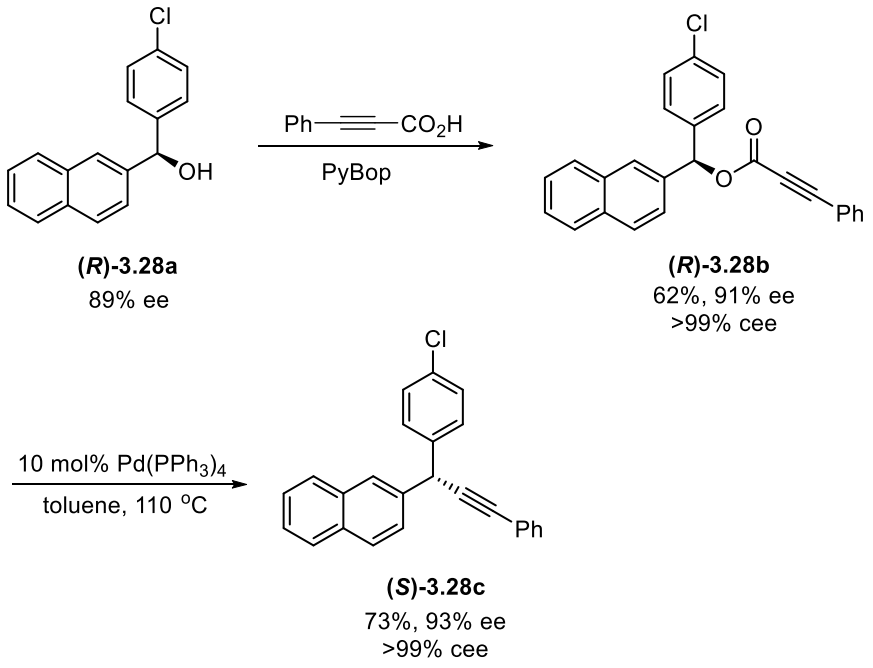




(*S*)-3.28c

Figure 3.4. X-ray crystal structure of **(*S*)-3.28c**

The absolute configuration of the alcohol **(*R*)-3.28a** was assigned as (*R*) by comparison with HPLC literature data.[33] Therefore, the absolute configuration of phenyl propiolate ester **(*R*)-3.28b** is (*R*). Since the absolute configuration of the product **(*S*)-3.28c** is (*S*), the decarboxylative benzylation of alkynes proceeds with inversion of configuration (Scheme 3.16).



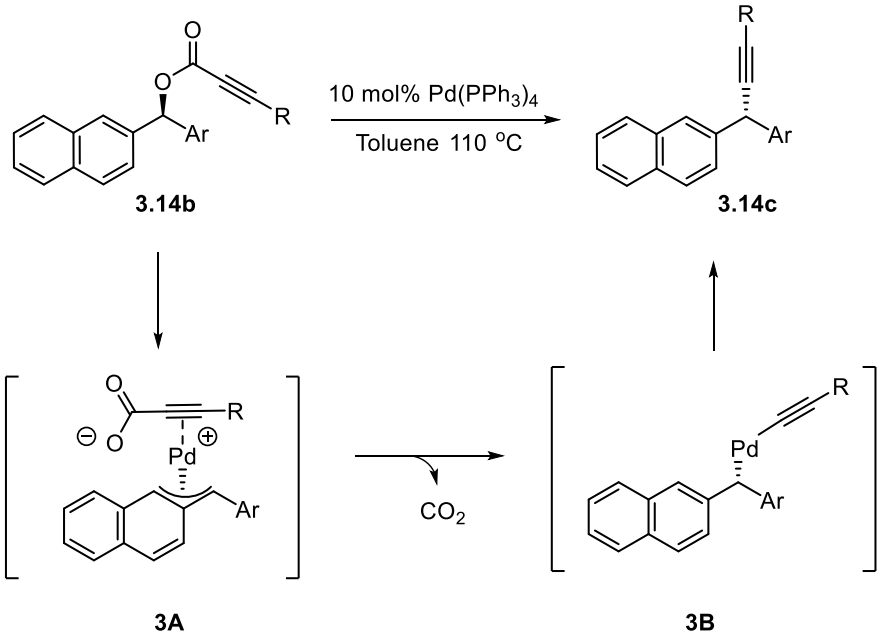
(*R*)-3.28a
89% ee

(*R*)-3.28b
62%, 91% ee
>99% cee

(*S*)-3.28c
73%, 93% ee
>99% cee

Scheme 3.16

The proposed catalytic cycle for the palladium-catalyzed stereospecific decarboxylative benzylation of alkynes is shown in scheme 3.17. Since the oxidative addition of benzyl ester **3.14b** with Pd(0) occurs via a S_N2-type displacement, the η^3-benzyl-Pd carboxylate intermediate (**3A**) is generated with inversion of stereochemistry.[4b] The formation of a cationic Pd-benzyl intermediate is further supported by the higher yield of the cross-coupled product obtained with electron rich substrates, due to the stabilization of the transition state in an S_N2 reaction. Decarboxylation of **3A** forms the benzyl-Pd-acetylide intermediate **3B**, which undergoes reductive elimination with retention of stereochemistry to give the cross-coupled product **3.14c**.



Scheme 3.17

The formation of the Pd-bound acetylide intermediate was previously proposed by Tunge *et al*., in a decarboxylative allyl-acetylide coupling.[34] Similarly, the observed (*S*) stereochemistry of the decarboxylated product **(*S*)-3.28c** supports the formation of a Pd-bound acetylide intermediate in the reaction mechanism.

In summary, this method allows the successful transfer of stereochemical information from a secondary alcohol to generate a tertiary stereogenic center. In addition, during the decarboxylative coupling a chiral Pd-π-benzyl intermediate is generated. This unique intermediate is equivalent to a chiral benzyl cation (Figure 3.5). Thus, the decarboxylative benzylation of alkynes is highly stereospecific. To the best of our knowledge, there are no reports on stereospecific decarboxylative benzylic cross-coupling reactions reported in literature. Unfortunately, this method is limited to substrates with extended aromatic systems (for example, 1-naphthyl, 2-naphthyl and indole), and could not be used for the synthesis of 1,1-diarylmethanes, that do not have extended arene systems. Additionally, this method provides an atom economical route for the asymmetric coupling of secondary benzylic electrophiles to alkynes.

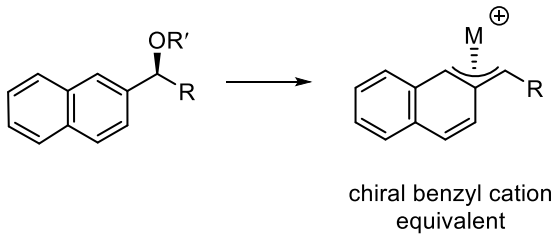


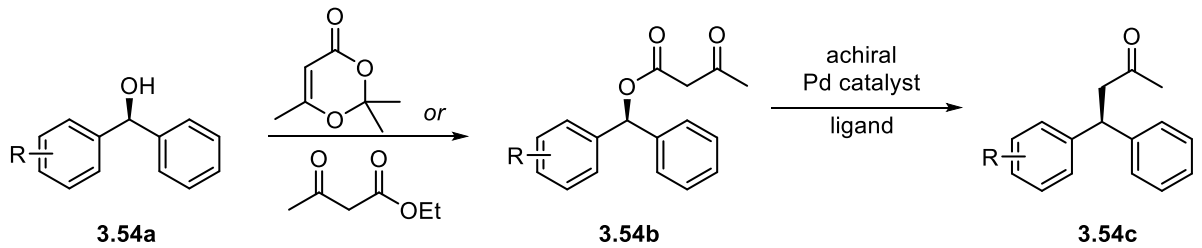
Figure 3.5

3.4.2 Development of stereospecific decarboxylative benzylation of ketones

The most general method to synthesize enantioenriched β,β-disubstituted ketones is the catalytic asymmetric 1,4-conjugate addition of boronic acids to α,β-unsaturated ketones, which is also known as the Hayashi-Miyaura reaction.[35] While rhodium is predominantly used,[36] use of less expensive palladium, in asymmetric conjugate addition of boronic acids to enones is far less developed and often suffers from poor enantioselectivity,[37] longer reaction times,[37a] and the need for organometallic additives.[38] Moreover, the use of asymmetric conjugate addition reactions to synthesize β,β-diaryl acyclic ketones have been rarely reported in literature.[39]

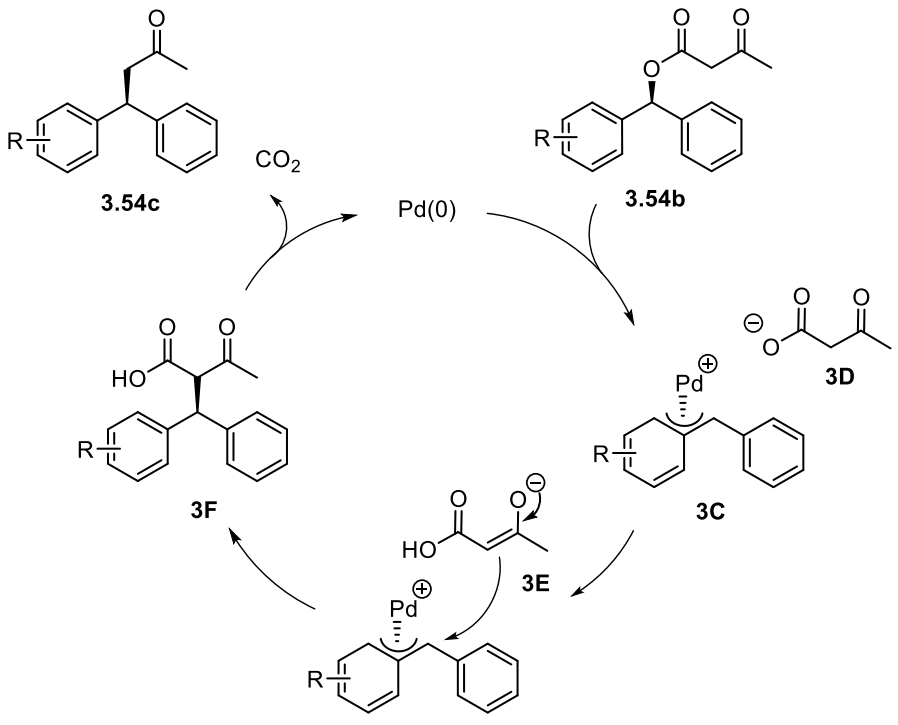
Previous reports on successful stereospecific allylation of ketone enolates via the palladium-catalyzed decarboxylative coupling of allyl β-ketoesters,[8-9] and racemic decarboxylative coupling of benzyl β-ketoesters,[27] prompted us to investigate the stereospecificity of the decarboxylative coupling of benzyl electrophiles with ketone enolates. We were interested in implementing a method to synthesize chiral benzylic ketones with a β,β-diaryl skeleton, specifically with aryl systems that do not have extended π-systems.

Similar to the stereospecific decarboxylative benzylation of alkynes, we envisioned the synthesis of enantioenriched benzyl β-ketoester **3.54b** from enantiopure diarylmethanols **3.54a**. In the presence of an achiral palladium catalyst, we expected the formation of non-racemic β,β-diaryl-benzylketone **3.54c** via the Pd-catalyzed decarboxylative coupling of **3.54b** (Scheme 3.18).



Scheme 3.18

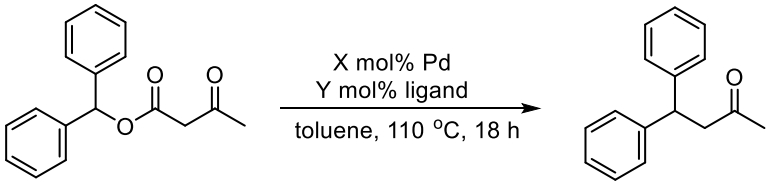
Ideally, the oxidative addition of enantioenriched benzyl ester **3.54b** to Pd(0) would generate the chiral palladium-π-benzyl intermediate **3C** with inversion of stereochemistry (Scheme 3.19). With allyl β-ketoester substrates that bear α-H's, allylation precedes decarboxylation,[40] implying, the carboxylate intermediate (**3D**) generated undergoes an intramolecular proton transfer to generate enolate carboxylic acid (**3E**). The experimental evidence for this type of intramolecular proton transfer was reported by Tunge *et al*. using a stereochemical test for palladium-catalyzed decarboxylative coupling of dihydrocoumarins.[40a] Moreover, the formation of diallylated products in decarboxylative allylation also supports this phenomenon.[41] Outer sphere attack of the enolate carboxylic acid intermediate **3E,** to the chiral palladium-π-benzyl intermediate **3C** would be expected to occur with inversion of stereochemistry,[42] which is followed by decarboxylation of **3F** to generate the chiral benzylated ketone **3.54c**. However, in the absence of α-H's in α,α-disubstituted enolates, decarboxylation precedes benzylation.



Scheme 3.19

To begin, we synthesized the benzyl β-ketoester **3.55b**, and examined the decarboxylative reaction with various Pd(0) catalysts, under different conditions. To our disappointment, none of the Pd(0) catalysts provided a satisfactory conversion to **3.55c**. Since cationic palladium sources have previously successfully coupled benzyl electrophiles that do not have extended π-systems,[43] we turned our attention to cationic palladium sources, and observed a satisfactory conversion to **3.55c** from many different cationic palladium species with different ligands (Table 3.7).

Table 3.7



3.55b **3.55c**

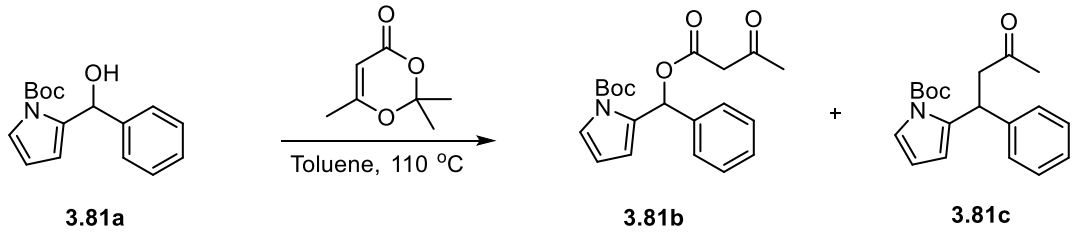
entry	X (mol%)	Pd	Y (mol%)	ligand	conversion (%)[a]
1	10	$Pd(PPh_3)_4$	-	-	0
2	10	CpPd(allyl)	11	Xantphos	0
3	5	Pd_2dba_3	10	Xantphos	0
4	5	Pd_2dba_3	20	XPhos	0
5	10	$[Pd(allyl)cod]BF_4$	20	XPhos	36
6	10	$[Pd(allyl)cod]BF_4$	11	dppf	0
7	10	$[Pd(allyl)cod]BF_4$	11	dppe	0
8	10	$[Pd(allyl)cod]SbF_6$	11	dppf	>99
9	10	$[Pd(allyl)cod]ClO_4$	11	dppf	0
10	10	[Pd(allyl)cod]OTf	11	dppf	>99
11	10	$[Pd(allyl)cod]PF_6$	11	dppf	0
12	10	[Pd(allyl)cod]OTf	20	$P(OPh)_3$	>99
13	10	$[Pd(allyl)cod]BF_4$	20	$P(OPh)_3$	93
14	10	$[Pd(allyl)cod]BF_4$	20	PPh_3	>99
15	10	$[Pd(allyl)cod]BF_4$	20	$P(1\text{-}Np)_3$	>99
16	10	$[Pd(allyl)cod]BF_4$	20	PMe_3	25
17	-	-	-	-	0

[a] Calculated using ^1H NMR

While the role of the counter ion for the cross-coupling is unknown, in the presence of 10 mol% $[Pd(allyl)cod]BF_4$ and 20 mol% $P(1\text{-}Np)_3$, (Table 3.6 , entry 15) the β-ketoester **3.55b** was

cleanly converted to the product **3.55c**, and it was isolated in 77% yield. Therefore, these reaction conditions were chosen as the optimized conditions. In the absence of the palladium source and the ligand we did not see any conversion of **3.55b** to the product (entry 17).

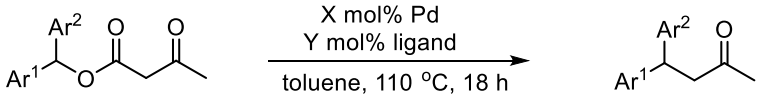
Next, we synthesized a variety of benzyl β-ketoesters (**3.56b - 3.80b**, Scheme 3.21).[44] The synthesis of β-ketoesters **3.56b - 3.80b** occurred cleanly. However, **3.81c** was isolated in the synthesis of β-ketoester **3.81b**. Presumably this product formed via a thermal decarboxylative rearrangement of **3.81b** (Scheme 3.20).



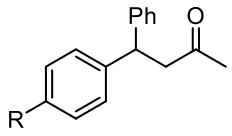
3.81a **3.81b** **3.81c**

Scheme 3.20

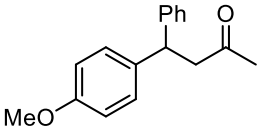
Moving forward, we then investigated the reactivity of benzyl β-ketoesters under the optimized conditions (Scheme 3.21). Similarly to previous projects, benzylated ketones were obtained in very high yield when electron donating substituents were present in the aryl systems. For example, **3.58c** was formed in 96% yield, when a *p*-OMe substituent was present. The presence of strong electron withdrawing substituents, for example, *p*-NO_2 (**3.63c**) and *p*-CN (**3.64c**), did not provide any product. However, the presence of *p*-OMe *and p*-NO_2 provided the benzylated ketone **3.68c** in good yield. The presence of chloro (**3.56c**) and bromo (**3.57c**) substituents was also tolerated and the respective benzyl ketones were obtained in moderate yields. Cyclic ketones could also be coupled, albeit in low yield (**3.69c**).



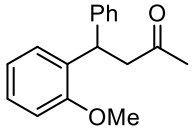
3.55b - 3.80b **3.55c - 3.80c**



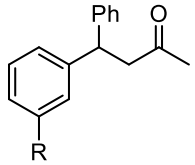
R = H 77% (**3.55c**)
R = Cl 57% (**3.56c**)
R = Br 50% (**3.57c**)



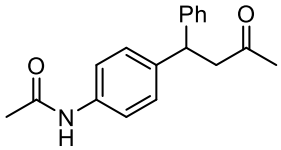
3.58c, 96%



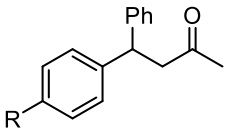
3.59c, 82%



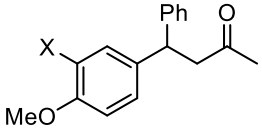
R = OMe 73% (**3.60c**)
R = CF_3 NR (**3.61c**)



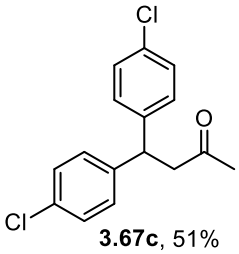
3.62c, 42%



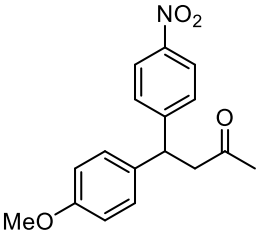
R = NO_2 NR (**3.63c**)
R = CN NR (**3.64c**)



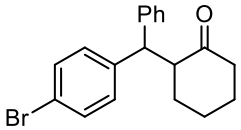
X = Br 70% (**3.65c**)
X = F 49% (**3.66c**)



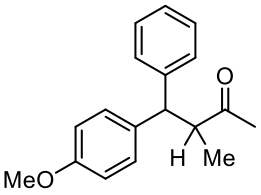
3.67c, 51%



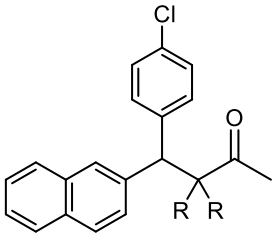
3.68c, 76%



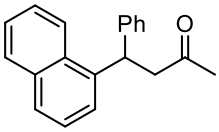
3.69c, 43%



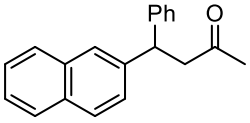
3.70c, 92%
dr 1 : 1.3



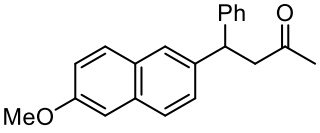
R = H 89%, **3.71c**
R = Me 88%, **3.72c**



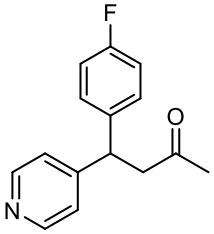
3.73c, 82%



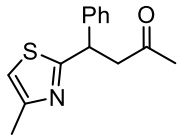
3.74c, 60%



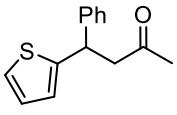
3.75c, 73%



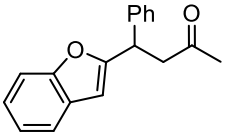
3.76c, NR



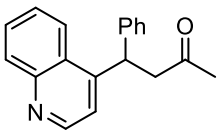
3.77c, 75%



3.78c, 70%



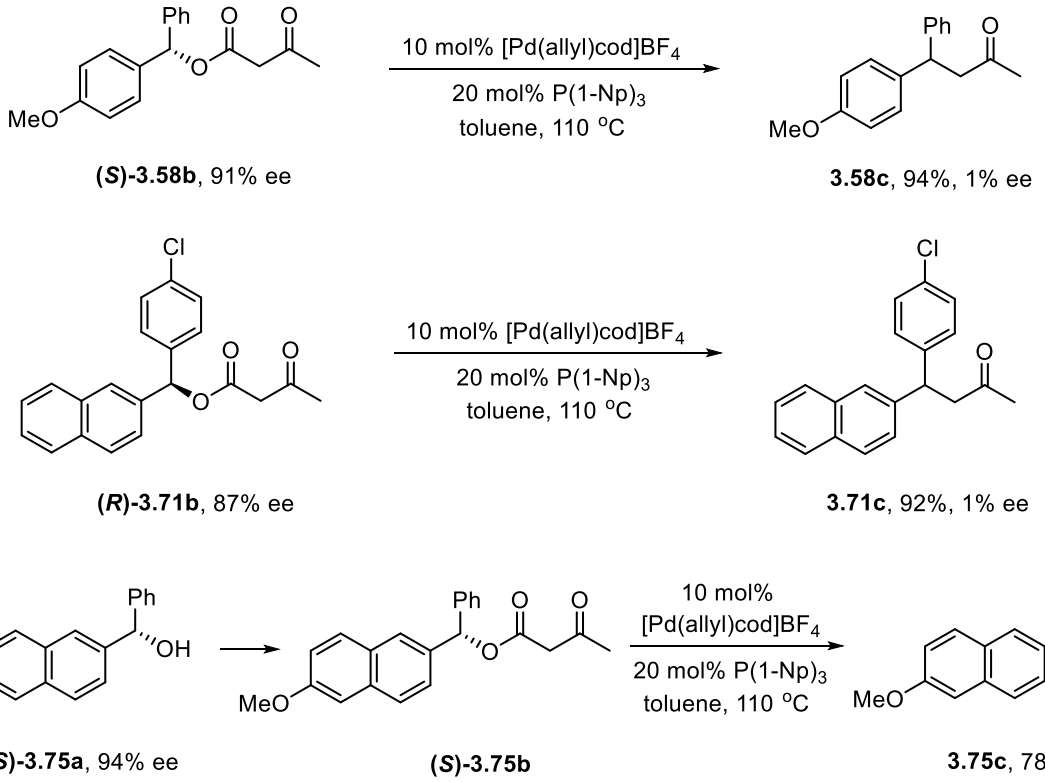
3.79c, 37%



3.80c, NR

Scheme 3.21

We were very pleased to obtain a high yield, in the formation of both α-mono (**3.70c**) and α,α-disubstitued (**3.72c**) benzyl ketones. The β-ketoesters with 1- and 2-naphthyl systems (**3.73c** and **3.74c**) also underwent decarboxylative coupling to yield benzylated ketones. Some heteroaromatic systems also underwent smooth coupling (**3.77c - 3.79c**), while β-ketoesters with pyridine (**3.76b**) and quinoline (**3.80b**) were unreactive.

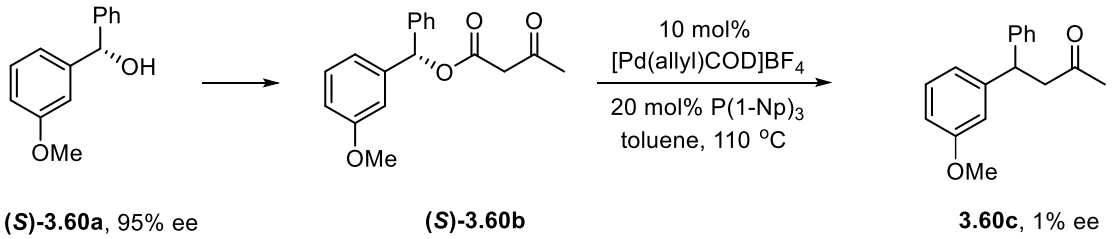


Scheme 3.22

Next, we synthesized several enantioenriched β-ketoesters to study the stereospecific cross-coupling reaction (Scheme 3.22). Under standard conditions, β-ketoesters underwent decarboxylative coupling to provide benzylated ketones. The synthesized benzylated ketones (**3.58c**, **3.71c**, **and 3.75c**) were purified by column chromatography and separated using chiral

stationary phase HPLC to determine the stereospecificity of the reaction. However, to our great disappointment, we repeatedly observed the formation of racemic ketones via the decarboxylative coupling of enantioenriched β-ketoesters.

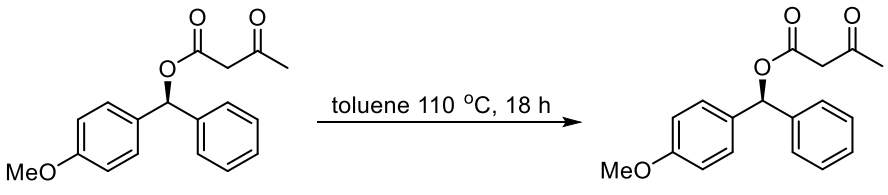
One hypothesis to explain the racemic products was that racemization of benzyl ketones occurred during the purification process on the silica column. Therefore, we separated the crude product **3.60c** by HPLC prior to purification. Again, the HPLC data showed a 1% ee (Scheme 3.23).



(***S***)-**3.60a**, 95% ee (***S***)-**3.60b** **3.60c**, 1% ee

Scheme 3.23

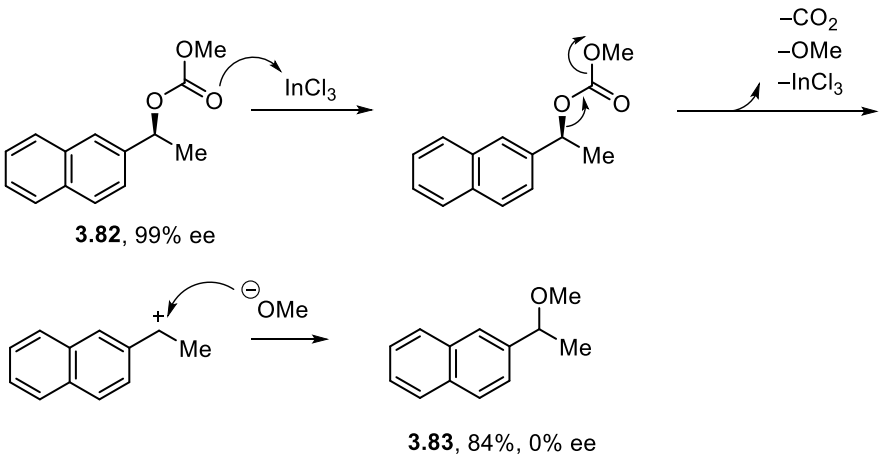
The possibility of the thermal racemization of the β-ketoester was also investigated since the reaction is performed at high temperature. In the absence of palladium, refluxing at 110 °C in toluene did not racemize the β-ketoester **(*S*)-3.58b**, nor did it undergo thermal decarboxylative benzylation (Scheme 3.24).



(***S***)-**3.58b**, 91% ee (***S***)-**3.58b**, 90% ee

Scheme 3.24

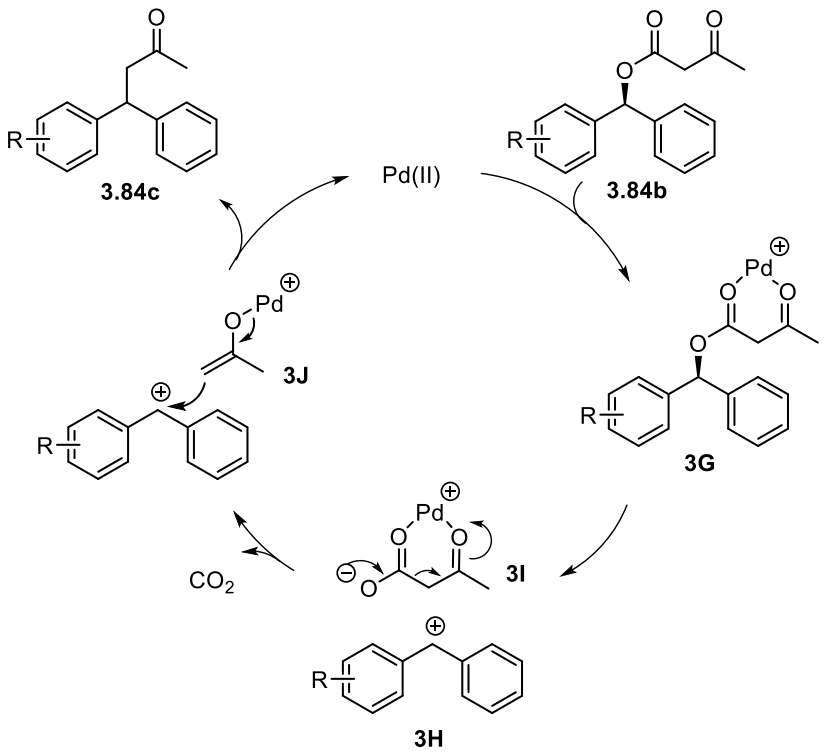
Since we always observed the formation of racemic benzylated ketones via the decarboxylative coupling of enantioenriched benzyl β-ketoesters (Scheme 3.22 and Scheme 3.23), we hypothesized the formation of an achiral secondary benzyl cation intermediate in the reaction mechanism. The Lewis acid promoted decarboxylative benzylic cross-coupling via the intermediacy of such an achiral benzyl cation has been reported in the literature.[45] Specifically, the formation of racemic benzylated product **3.83** was observed when enantioenriched benzyl carbonate **3.82** was used (Scheme 3.25).



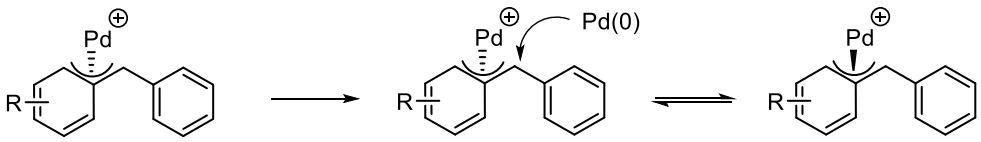
Scheme 3.25

Therefore, we propose that in the catalytic cycle (Scheme 3.26) the carbonyl coordination to cationic palladium facilitates the ionization of **3G**, giving rise to an achiral benzyl cation **3H** and carboxylate intermediate **3I**. Decarboxylation of **3I** generates the enolate nucleophile **3J** which reacts with the benzyl carbocation to generate the racemic benzylated ketone **3.84c** through an S_N1-type mechanism.

While the aforementioned catalytic pathway is mostly viable for obtaining a racemic benzylated ketone, we cannot completely rule out the epimerization of the chiral palladium-π-benzyl intermediate via the attack of a second Pd(0) species (Scheme 3.27).[11]



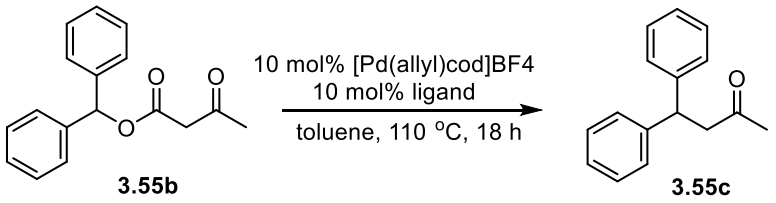
Scheme 3.26



Scheme 3.27

Next, we tried to optimize the reaction conditions with the racemic-**3.55b** to implement an enantioconvergent reaction using chiral ligands (Table 3.8, Figure 3.6). While most of the chiral ligands resulted poor conversion to product, the use of (*R*)-3,4,5-MeO-MeOBIPHEP provided a 77% conversion to **3.55c** with very low enantiomeric excess (Table 3.8, entry 3).

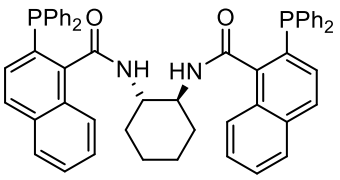
Table 3.8



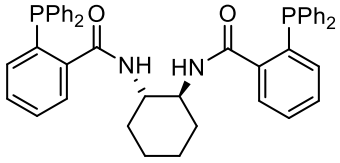
3.55b **3.55c**

entry	chiral ligand	conversion (%)[a]	% ee of [b]
1	(*S*,*S*)-DACH-naphthyl Trost Ligand	3	-
2	(*S*,*S*)-DACH-phenyl Trost Ligand	1	-
3	(*R*)-3,4,5-MeO-MeOBIPHEP	77	4
4	(*R*)-(*S*)-Josiphos	44	1
5	(*R*)-*i*Pr-MeOBIPHEP	8	-

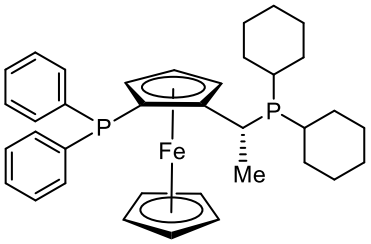
[a]Calculated from ^{1}H NMR, [b]In entry 3 and 4, enantiomers of the product were separated by HPLC.



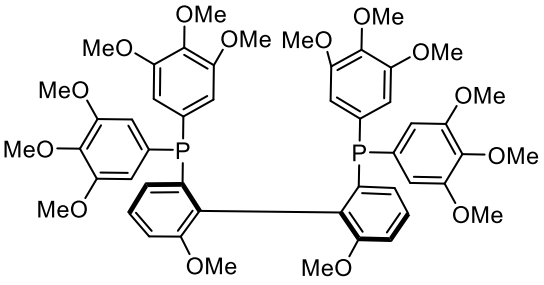
(*S*,*S*)-DACH-naphthyl Trost Ligand



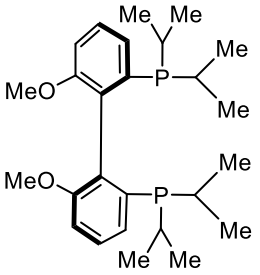
(*S*,*S*)-DACH-phenyl Trost Ligand



(*R*)-(*S*)-Josiphos



(*R*)-3,4,5-MeO-MeOBIPHEP

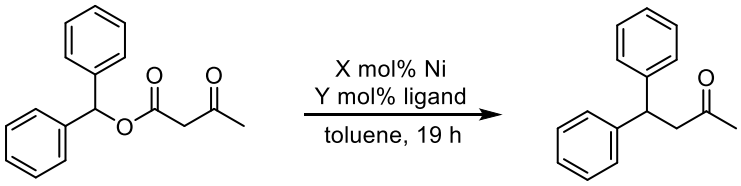


(*R*)-*i*-Pr-MeOBIPHEP

Figure 3.6

Since there are reports on successful stereospecific benzylic cross-coupling reactions using nickel catalysts, we then screened nickel catalysts with different mono- and bidentate ligands (Table 3.9). However, many of the catalyst/ligand combinations failed to provide a satisfactory conversion to the benzylated ketone **3.55c**, while benzyl β-ketoester **3.55b** remained unchanged. Nevertheless, $Ni(cod)_2$ and tri(2-furyl)phosphine provided a 68% conversion to the product when the reaction was heated at 160 °C for 40 hours (entry 7, Table 3.9).

Table 3.9

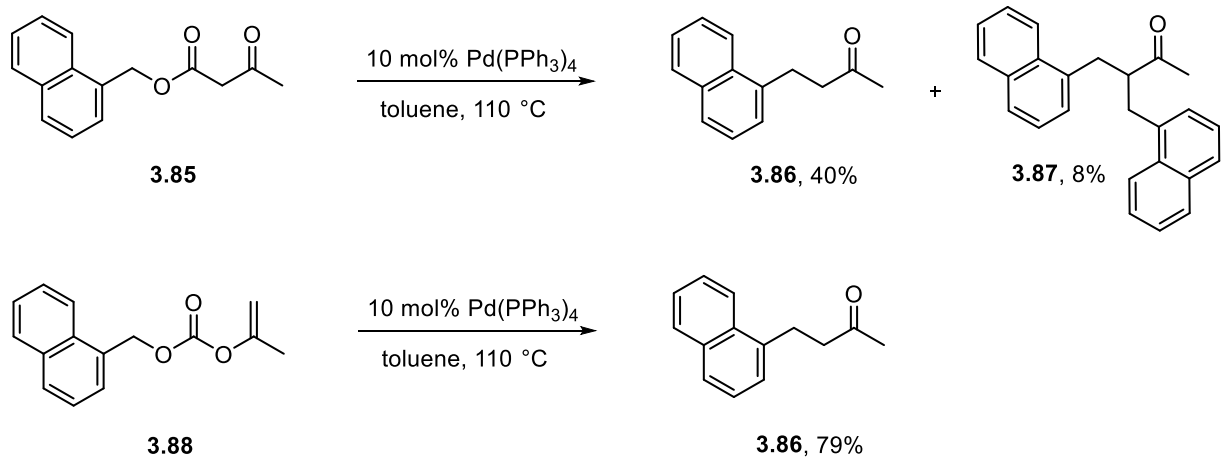


3.55b **3.55c**

entry	X (mol%)	Ni	Y (mol%)	ligand	temp. (°C)	conversion (%)[a]
1	10	$Ni(cod)_2$	20	PCy_3	rt	0
2	10	$Ni(cod)_2$	20	PCy_3	70	0
3	10	$Ni(cod)_2$	20	Tri-*o*-tolylphosphine	70	0
4	10	$Ni(cod)_2$	20	$MePh_2P$	70	0
5	10	$Ni(cod)_2$	20	tris-2,4,6-trimethoxyphenylphosphine	70	0
6	10	$Ni(dppe)_2Cl_2$	-	-	rt	0
7	10	$Ni(cod)_2$	20	tri(2-furyl)phosphine	160	16 (68)[b]
8	10	$Ni(cod)_2$	20	$P(OPh)_3$	160	0
9	10	$Ni(cod)_2$	20	PCy_3	160	1
10	10	$Ni(cod)_2$	20	tris-2,4,6-trimethoxyphenylphosphine	160	0
11	10	$Ni(cod)_2$	20	tri(2-furyl)phosphine	110	0
12	10	$Ni(cod)_2$	20	tri(2-furyl)phosphine	110	10
13	10	$Ni(cod)_2$	11	*rac*-BINAP	160	13
14	10	$Ni(cod)_2$	11	Xantphos	160	1
15	10	$NiCl_2(dppf)$	10	dppf	160	1

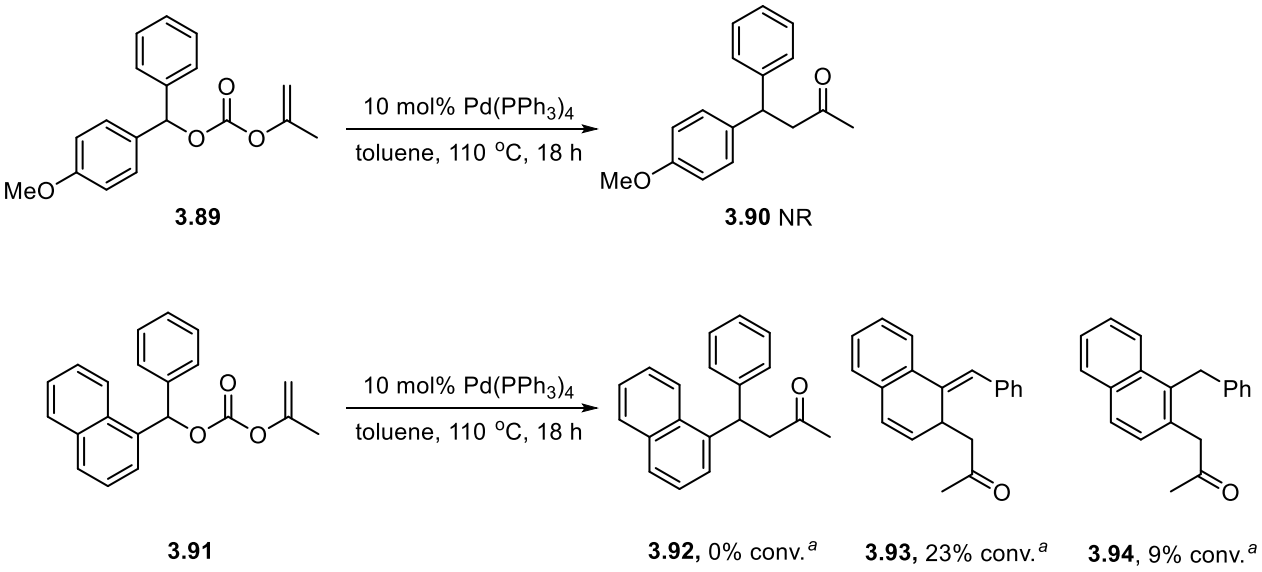
[a]Calculated from ^1H NMR, all the reactions were performed in 10 mg scale. [b]Yield after 40 h of reaction.

Because benzyl β-ketoesters were unsuccessful in stereospecific decarboxylative benzylation, we turned our attention to benzyl enol carbonates. Literature reports on successful allylation of ketones via the decarboxylative cross-coupling of allyl enol carbonates,[46] and the previous observations by a former coworker in the Tunge group (Robert Torregrosa, Scheme 3.28),[47] prompted us to look at the reactivity of benzyl enol carbonates. In his report, under identical conditions he observed the formation of the benzylated ketone **3.86** in 40% and in 79% yield, via the decarboxylative coupling of benzyl β-ketoester **3.85**, and benzyl enol carbonate **3.88** respectively. With benzyl β-ketoesters a dibenzylated ketone **3.87** was also formed in low yield.



Scheme 3.28

Next, we synthesized the benzyl enol carbonates **3.89** and **3.91** and subjected these to the identical reaction conditions reported by Torregrosa (Scheme 3.29).[47] While benzyl enol carbonate **3.89** was unable to undergo decarboxylative benzylation under these conditions, it was interesting to see a very clean conversion of **3.91** to two different products **3.93** and **3.94** albeit in very low yield. However, we did not observe the formation of the expected β,β-disubstituted ketone **3.92** via the decarboxylative benzylation of **3.91**.



[a] % conversion calculated by ^{1}H NMR.

Scheme 3.29

In summary, the unavoidable racemization of β-ketoesters in the presence of cationic palladium prevented us from developing a stereospecific decarboxylative benzylation reaction with enolate nucleophiles. However, the optimized conditions could be used to synthesize racemic α,α-disubstituted-β,β-diaryl acyclic ketones in high yield. Additionally, our studies show that the decarboxylative cross-coupling of "simple" benzyl esters is much more challenging compared to the benzyl esters that have extended arenes.

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Appendix A2

General Information:

All reactions were run under an argon atmosphere using standard Schlenk techniques or an inert atmosphere glove box. All glassware were oven or flame dried prior to use. Toluene and THF were dried over sodium and distilled in the presence of benzophenone. Dried toluene was taken to the glove box in a Schlenk flask with activated molecular sieves. CH_2Cl_2 was dried over alumina. Other commercially available solvents were used without additional purification. All palladium catalysts and ligands were purchased from Strem and stored in the glove box under an argon atmosphere. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity silica obtained from Sorbent Technologies.

^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer equipped with a QNP cryoprobe and referenced to residual protio solvent signals. Structural assignments were based on ^{1}H, ^{13}C, DEPT-135, COSY, HSQC. Mass spectrometry was run using EI or ESI techniques. Chiral HPLC analysis was performed by LC-$10AT_{VP}$ Shimadzu HPLC using Chiralpak AD, AS-H, AD-H and Chiralcel OD-H, OD chiral columns (0.46 cm x 25 cm), eluting with hexane/*iso*-propanol mixture. Optical rotations were measured on an Autopol® IV automatic polarimeter using a 5 cm cell and sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated.

Synthesis of racemic diarylmethanols:

Racemic diarylmethanols were prepared by methods reported in literature.[1]

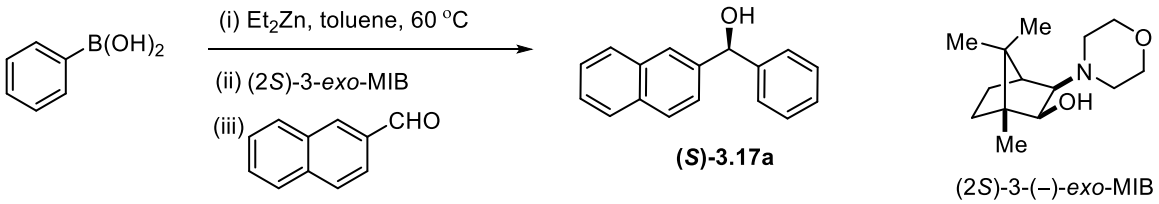
Synthesis of racemic benzyl propiolates:

Racemic propiolic esters were prepared by standard DCC, DMAP coupling as outlined in literature.[2]

Synthesis of asymmetric diarylmethanols:

All the enantioenriched diarylmethanols were prepared by slightly modifying the procedure reported by Braga.[3] (2*S*)-(–)-3-*exo*-MIB was synthesized using (*R*)-Camphor in three steps according to a method outlined in literature.[4]

Representative procedure for the synthesis of asymmetric diarylmethanols:



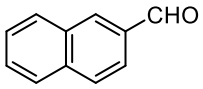
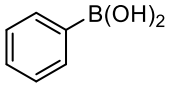
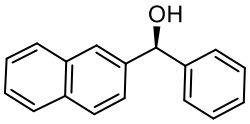
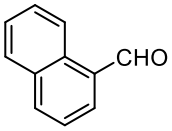
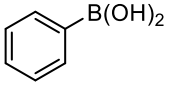
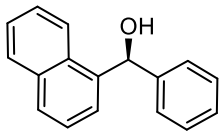
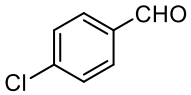
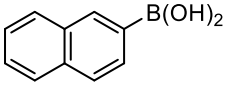
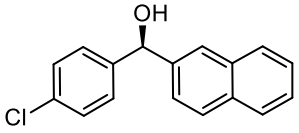
To a flame dried Schlenk flask was added phenyl boronic acid (6 mmol, 731 mg) and toluene (10 mL). Then, diethyl zinc (18 mmol, 18 mL, 1.0 M in hexanes) was added and the solution was heated at 60 °C for 24 hours in an oil bath. After 24 hours, it was removed from the oil bath and cooled to room temperature. Then, a solution of (2*S*)-(–)3-*exo*-MIB (0.25 mmol, 59.8 mg) in toluene (5 mL) was added to the reaction mixture and was allowed to stir for one hour at room temperature, before the addition of 2-naphthaldehyde (2.5 mmol, 390 mg). Then the reaction mixture was allowed to stir for 12 hours and the resulting mixture was quenched with 1 N HCl

acid, and the product was extracted with EtOAc. The Combined organics were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via flash chromatography over silica gel.

Assigning the absolute configuration to enantioenriched diarylmethanols:

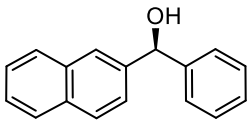
Absolute configuration of the enantiopure diaryl alcohols were assigned based on HPLC literature data (Table A2.1).[5] Absolute configuration for all other alcohols could be assigned in an analogous manner.

Table A2.1

aldehyde used	boronic acid used	absolute configuration of alcohol[a]	Obtained alcohol
		(***S***)-**3.17a**	
		(***S***)-**3.15a**	
		(***R***)-**3.28a**	

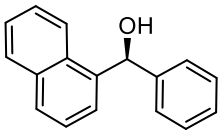
[a] HPLC data are provided

HPLC data for the enantioenriched diarylmethanols:



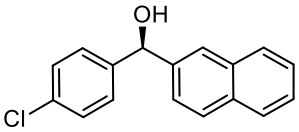
(*S*)-naphthalen-2-yl(phenyl)methanol ((*S*)-3.17a)

HPLC analysis: 91 %ee (Chiralcel OD, 95:5 Hexanes/isopropanol, 0.8 mL/min, 254 nm, major R*t* = 31.5 min, minor R*t* 39.7 min).



(*S*)-naphthalen-1-yl(phenyl)methanol ((*S*)-3.15a)

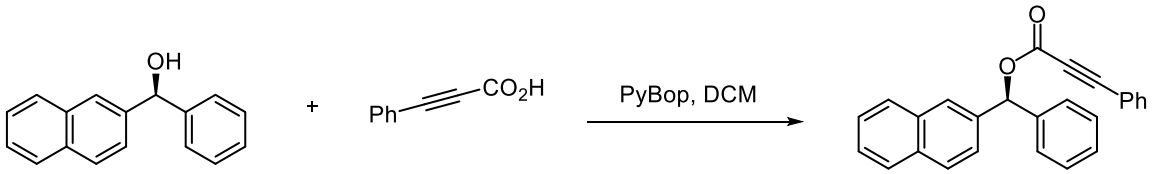
HPLC analysis: 93% ee (Chiralcel OD, 80:20 Hexanes/isopropanol, 0.8 mL/min, 254 nm, major R*t* = 10.8 min, minor R*t* 21.9 min).



(*R*)-(4-chlorophenyl)(naphthalen-2-yl)methanol ((*R*)-3.28a)

HPLC analysis: 89% ee (Chiralcel OD-H, 90:10 Hexanes/isopropanol, 0.8 mL/min, 254 nm, major R*t* = 20.4 min, minor R*t* = 18.3 min).

Representative procedure for the synthesis of enantioenriched benzyl phenyl propiolates:

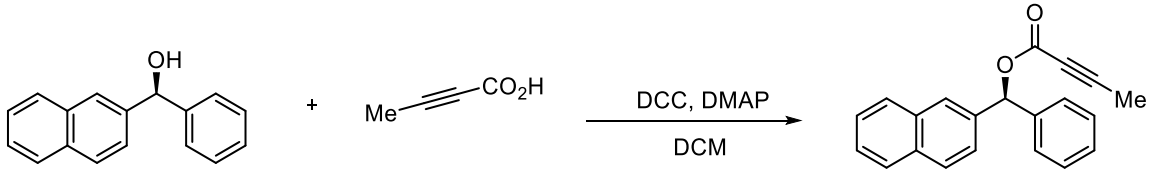


(*S*)-3.17a **(*S*)-3.17b**

To a flame dried Schlenk flask with a stir bar was added phenylpropiolic acid (222 mg, 1.5 mmol) in 0.50 M DCM and triethyl amine (0.2 ml, 1.5 mmol). This reaction mixture was cooled in a dry ice/xylene bath, before the addition of the enantioenriched diaryl alcohol **(*S*)-3.17a** (356 mg, 1.5

mmol) in 0.50 M DCM. After 15 min of stirring, PyBop (780 mg, 1.5 mmol) in 0.50M DCM was added to the reaction mixture and left for overnight stirring with gradual warming to room temperature. The resulting mixture was quenched with $NaHCO_3$ and extracted with DCM. Combined organics were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via flash chromatography over silica gel.

Representative procedure for the synthesis of the other benzyl propiolates ((*R*)-3.44b-(*R*)-3.49b):



(*S*)-3.17a (*S*)-3.44b

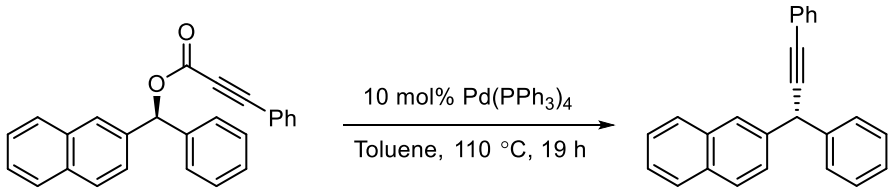
An oven dried reaction flask was charged with the enantioenriched diaryl alcohol **(*S*)-3.17a** (437mg, 1.86 mmol) and 2-butynoic acid (156mg, 1.86 mmol) in 0.2 M DCM, and this reaction mixture was cooled in an ice bath for 30 minutes. A solution of DCC (383.7 mg, 1.86 mmol) and DMAP (22.7 mg, 0.186 mmol) was dissolved in DCM (9 mL) and added drop wise to the cooled reaction mixture and allowed for gradual warming to room temperature. The reaction was stirred overnight at room temperature. The resulting mixture was diluted with DCM and filtered through celite. The celite pad was washed with small portions of DCM. Collected filtrate was concentrated *in vacuo* and purified via flash chromatography over silica gel.

Preparation of propiolic acid for (*S*)-3.47b - (*S*)-3.49b:

These compounds were made by the method outlined by Tanaka.[6]

Phenyl propiolic acid, 2-butynoic acid and 2-hexynoic acid were purchased from Sigma Aldrich.

Representative procedure for the palladium catalyzed decarboxylative benzylation of alkynes:



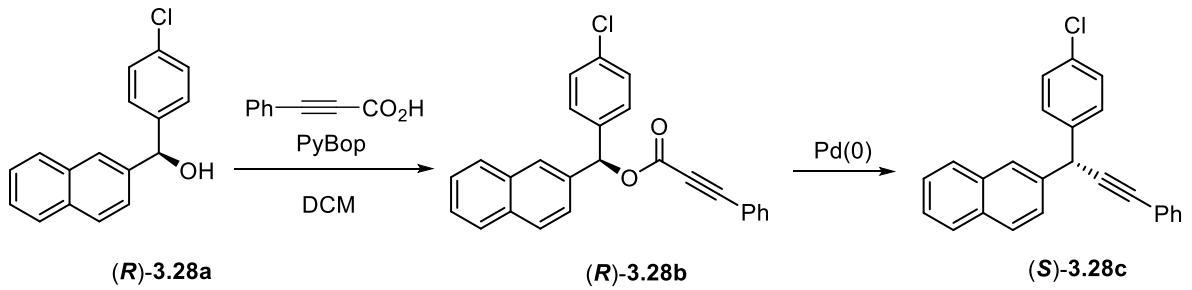
(*S*)-3.17b (*R*)-3.17c

In a glove box, under an argon atmosphere, a flame dried Schlenk tube was charged with propiolic ester **(*S*)-3.17b** (80 mg, 0.22 mmol), $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) and toluene (5.5 mL). The Schlenk tube was equipped with a septum, and the sealed tube was removed from the glove box and stirred at 110 °C for 19 hours. The resulting reaction mixture was cooled to room temperature, concentrated *in vacuo* and was purified via flash chromatography over silica gel. The isolated compound was stored in the freezer.

Note on storage:

We observed a loss in %ee in propiolic esters when stored at room temperature for longer period of time. Therefore, all the propiolic esters and benzyl alkynes were stored in a freezer upon isolation.

Demonstration of the stereochemical course:



(***R***)-**3.28a** (***R***)-**3.28b** (***S***)-**3.28c**

Enantioenriched alcohol **(*R*)-3.28a** was prepared by a slightly modified procedure reported by Braga,[3] using (2*S*)-3-*exo*-MIB as the chiral catalyst. The stereochemistry of (*R*)-**3.28a** was verified by comparison of the HPLC data to the reported data in literature.[5c] Conversion to benzyl phenylpropiolate (*R*)-**3.28b** was followed by the palladium catalyzed stereospecific cross-coupling reaction, to generate (*S*)-**3.28c**, in which the absolute configuration was determined by x-ray crystallographic analysis. This product corresponds to a net inversion of stereochemistry in this stereospecific cross-coupling reaction. The absolute configuration of all the decarboxylated products were assigned based on the assumption that the cross-coupling reaction occurs with inversion of configuration.

Determination of the absolute configuration of (*S*)-3.28c:

The absolute configuration of compound **(*S*)-3.28c** was determined using anomalous dispersion of the Cu Kα x-rays. The value of the Flack absolute structure parameter refined to a value of 0.045(15) using all of the reflections and to a value of 0.092(10) using 652 selected quotients with the Parsons' Method.[7] This was further checked by refining a BASF parameter [final value: 0.060(17)] for an inversion twin operation. Crystal data and refinement for $C_{25}H_{17}Cl$ is listed in Table A2.2.

Table A2.2. Crystal data and structure refinement for $C_{25}H_{17}Cl$.

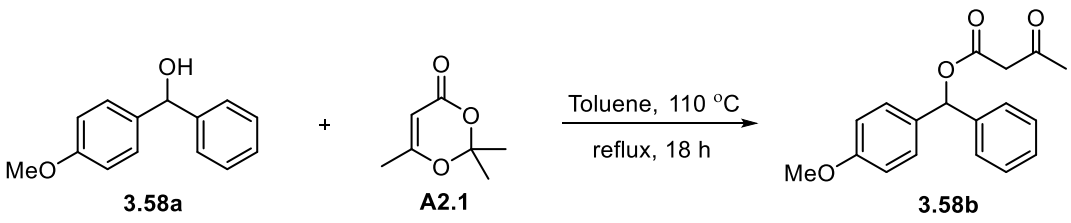
Empirical formula	$C_{25}H_{17}Cl$	
Formula weight	352.83	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 10.027(2) Å	α = 90°.
	b = 5.4598(13) Å	β = 106.348(4)°.
	c = 16.953(4) Å	γ = 90°.
Volume	890.6(4) $Å^3$	
Z	2	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	1.909 mm^{-1}	
F(000)	368	
Crystal size	0.360 x 0.085 x 0.050 mm^3	
Theta range for data collection	4.595 to 68.042°.	
Index ranges	-11<=h<=10, -5<=k<=6, -19<=l<=20	
Reflections collected	5823	
Independent reflections	2388 [R(int) = 0.0264]	
Completeness to theta = 66.000°	97.8 %	
Absorption correction	Multi-scan	

Max. and min. transmission	1.000 and 0.676
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2388 / 1 / 303
Goodness-of-fit on F^2	1.065
Final R indices [I>2sigma(I)]	R1 = 0.0255, wR2 = 0.0661
R indices (all data)	R1 = 0.0255, wR2 = 0.0661
Absolute structure parameter	0.092(10)
Extinction coefficient	n/a
Largest diff. peak and hole	0.153 and -0.211 e.$Å^{-3}$

Representative procedure for the synthesis of racemic or enantioenriched benzyl β-ketoesters:

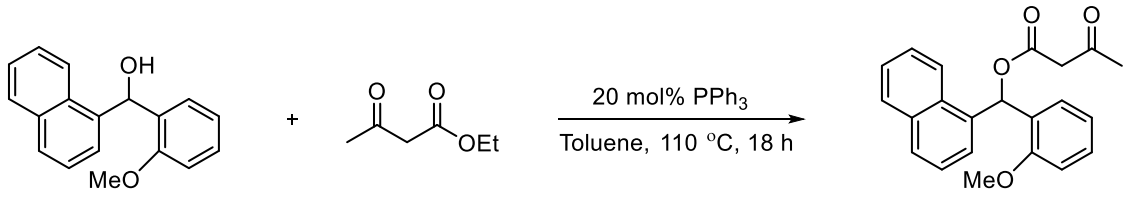
Initially 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (**A2.1**) (purchased from Sigma Aldrich) was used for the synthesis of β-ketoesters (Method 1), but since the reagent (**A2.1**) was discontinued by Sigma, ethyl acetoacetate was used in the presence of catalytic amount of PPh_3 (Method 2) to synthesize β-ketoesters via the transesterification of alcohols.

Method 1:[7]



An oven dried flask was charged with diarylmethanol **3.58a** (275 mg, 1.28 mmol) and was dissolved in toluene (7 mL). 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (0.18 mL, 1.41 mmol) was added to the reaction mixture and refluxed for 18 hours. The resulting reaction mixture was cooled to room temperature and concentrated *in vacuo* and was purified via flash chromatography over silica gel.

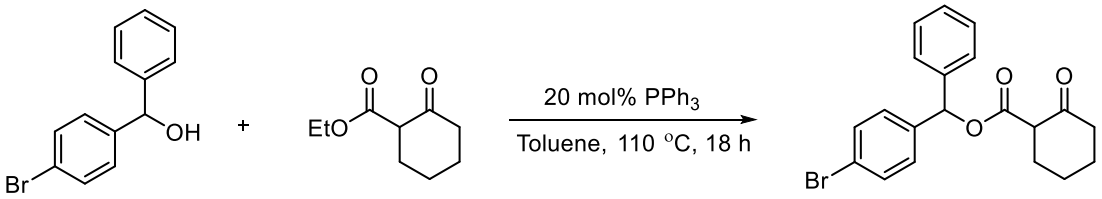
Method 2:[8]



3.59a **3.59b**

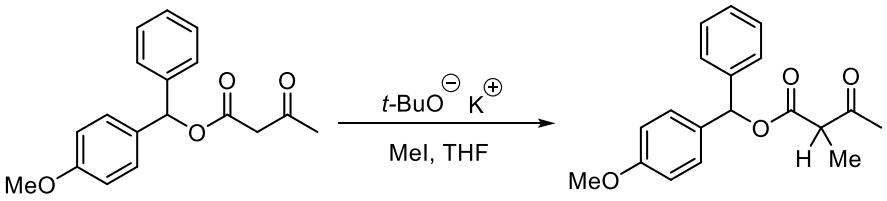
An oven died flask was charged with diarylmethanol **3.59a** (300 mg, 1.13 mmol), ethyl acetoacetate (0.13 mL, 1.03 mmol), triphenylphosphine (54 mg, 0.21 mmol) and toluene (11 mL). Then the reaction mixture was refluxed for 18 h. The resulting mixture was then concentrated *in vacuo* and purified via flash chromatography over silica gel.

Cyclic β-ketoester **3.69b** was synthesized by the transesterification of the respective alcohol **3.69a** with ethyl 2-oxocyclohexane-1-carboxylate (**A2.3**), following method 2.



3.69a **A2.3** **3.69b**

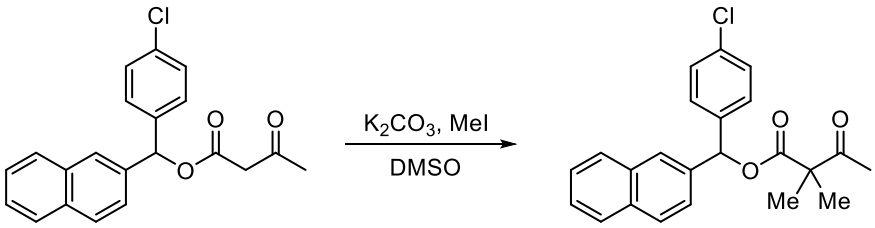
Synthesis of α-mono substituted β-ketoesters:



3.70b **3.70b'**

In a glove box, an oven dried flask was charged with potassium *tert*-butoxide (84.2 mg, 0.75 mmol). The flask was sealed and was taken out of the glove box. The β-ketoester **3.70b** (320 mg, 1.07 mmol) was dissolved in THF (5 mL) and added to the sealed flask. The reaction mixture was cooled to 0 °C. This was then followed by the dropwise addition of methyl iodide (0.06 mL, 1.07 mmol) and the reaction was allowed to run overnight. When the reaction was completed, it was quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine and died over $MgSO_4$. The filtrate was concentrated and purified via flash chromatography over silica gel.

Synthesis of α,α-dimethyl substituted β-ketoesters:

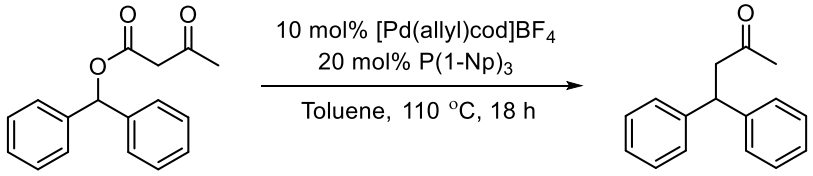


3.72b **3.72b'**

An oven dried flask was charged with the β-ketoester **3.72b** (323 mg, 0.91 mmol) and DMSO (18 mL). Activated K_2CO_3 (503 mg, 3.64 mmol) was added after few minutes and the reaction was stirred at room temperature for 30 minutes. This was followed by the dropwise addition of

iodomethane (0.11 mL, 1.82 mmol). The resulting mixture was stirred overnight at room temperature and the resulting solution was quenched with water. The product was extracted with DCM two times. Combined organics were washed with brine and dried over anhydrous MgSO4. The collected filtrate was concentrated *in vacuo* and purified via flash chromatography over silica gel.

Representative procedure for the palladium catalyzed decarboxylative benzylation of ketones:

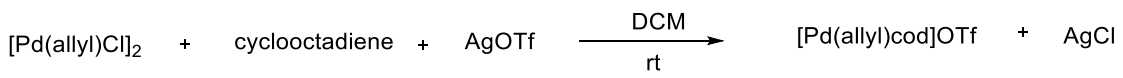


3.55b **3.55c**

In a glove box, a Schlenk flask with a stir bar was charged with the β-ketoester **3.55b** (100 mg, 0.37 mmol), $[Pd(allyl)cod]BF_4$ (12.7 mg, 0.037 mmol), tri-1-naphthylphosphine (30.68 mg, 0.074 mmol) and toluene (12.4 mL). The flask was sealed with a septum and taken out of the glove box and the reaction was allowed to run in an oil bath set to 110 °C. After 18 h, the resulted reaction mixture was concentrated *in vacuo* and purified via flash chromatography over silica gel.

Representative procedure for the synthesis of palladium sources:

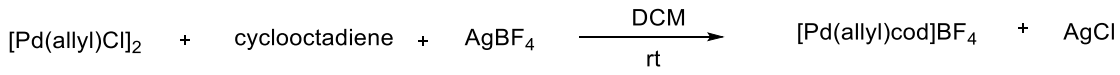
Synthesis of [Pd(allyl)cod]OTf (SM-1-173):



In a glove box, an oven dried Schlenk flask with a stir bar was charged with allylpalladium(II) chloride dimer (100 mg, 0.27 mmol), silver triflate (140.3 mg, 0.55 mmol) and DCM (5 mL). The

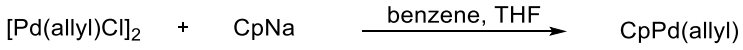
flask was sealed with a septum, taken out from the glove box, and allowed to stir for 15 minutes before the addition of cyclooctadiene (0.07 mL, 0.55 mmol). The reaction was stirred for 5 more minutes and filtered. The filter cake was then washed with more DCM. Then diethyl ether was added to the filtrate until a precipitate formed. Then this was filtered, and the collected solid on the filter paper was quickly transferred to a vial and dried under vacuum. The vial was taken into the glove box, and stored in glove box freezer.

Synthesis of [Pd(allyl)cod]BF_4 (SM-1-229):



The above procedure reported for [Pd(allyl)cod]OTf was followed, using $AgBF_4$.

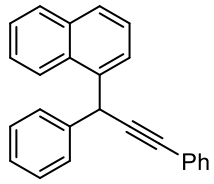
Synthesis of CpPd(allyl) (SM-2-174):



In a glove box, an oven dried Schlenk flask was charged with allylpalladium(II) chloride dimer (797 mg, 2.18 mmol), benzene (10 mL) and THF (10 mL). The flask was sealed with a septum and taken out of the glove box. The reaction mixture was cooled to -5 °C, before the drop wise addition of sodium cyclopentadienide - 2M in THF (2.18 mL, 4.36 mmol), The reaction was allowed to run for 1 hour at -5 °C, and then the ice bath was removed. The reaction was stirred another 30 minutes at room temperature, and then the resulting reaction mixture was filtered. The solid collected was washed with pentane, transferred to a vial and dried under vacuum. Then the vial was taken into the glove box and stored in the glove box freezer.

Synthesis of benzyl enol carbonates **3.89** and **3.91**, and all the reaction procedures and characterization data are detailed in appendix A3.

Characterization data for racemic benzyl alkynes:



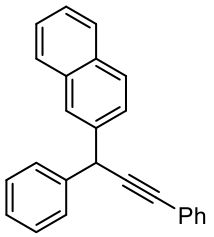
1-(1,3-diphenylprop-2-yn-1-yl)naphthalene (3.15c)

White solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 6.4, 3.4 Hz, 1H), 7.89 (dt, *J* = 7.0, 3.5 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.47 (dd, *J* = 6.3, 3.3 Hz, 4H), 7.37 – 7.32 (m, 2H), 7.32 – 7.27 (m, 4H), 7.24 (d, *J* = 7.4 Hz, 1H), 5.95 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.21, 137.04, 134.32, 131.86, 131.19, 128.99, 128.75, 128.37, 128.28, 128.19, 128.14, 127.04, 126.91, 126.30, 125.79, 125.69, 124.36, 123.69, 90.45, 85.44, 40.95.

HRMS calcd for $C_{25}H_{18}$ [M+] 318.1409, found 318.1387.



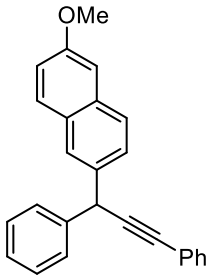
2-(1,3-diphenylprop-2-yn-1-yl)naphthalene (3.17c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.8 Hz, 1H), 7.85 – 7.77 (m, 3H), 7.54 – 7.48 (m, 5H), 7.46 (td, *J* = 7.0, 1.6 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.32 (dd, *J* = 4.7, 2.1 Hz, 3H), 7.24 (d, *J* = 7.4 Hz, 1H), 5.38 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.68, 139.28, 133.60, 132.63, 131.90, 128.83, 128.63, 128.44, 128.23, 128.21, 128.10, 127.81, 127.16, 126.50, 126.46, 126.36, 126.01, 123.64, 90.22, 85.43, 44.06.

HRMS calcd for $C_{25}H_{18}Na$ [M+Na] 341.1306, found 341.1301.



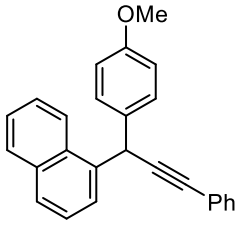
2-(1,3-diphenylprop-2-yn-1-yl)-6-methoxynaphthalene (3.18c)

Yellow liquid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.82 (m, 1H), 7.71 (dd, *J* = 15.8, 8.8 Hz, 2H), 7.54 – 7.50 (m, 3H), 7.49 (d, *J* = 1.5 Hz, 2H), 7.37 – 7.29 (m, 5H), 7.28 – 7.21 (m, 1H), 7.19 – 7.10 (m, 2H), 5.36 (s, 1H), 3.91 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.83, 141.89, 137.02, 133.73, 131.90, 129.56, 129.03, 128.79, 128.42, 128.18, 127.48, 127.09, 127.00, 126.30, 123.69, 119.11, 105.83, 90.43, 85.27, 55.49, 43.87.

HRMS calcd for $C_{26}H_{20}O$ [M+] 348.1514, found 348.1504.



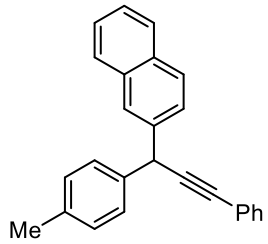
1-(1-(4-methoxphenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.19c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.7 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 1.3 Hz, 1H), 7.53 – 7.42 (m, 5H), 7.41 – 7.34 (m, 2H), 7.32 – 7.27 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.89 (s, 1H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.59, 137.29, 134.31, 133.32, 131.84, 131.17, 129.19, 128.98, 128.36, 128.20, 128.09, 126.71, 126.26, 125.76, 125.68, 124.37, 123.74, 114.10, 90.76, 85.21, 55.43, 40.15.

HRMS calcd for $C_{26}H_{19}O$ [M-H] 347.1436, found 347.1429.



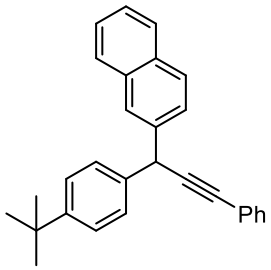
2-(3-phenyl-1-(p-tolyl)prop-2-yn-1-yl)naphthalene (3.20c)

Colorless oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 1.8 Hz, 1H), 7.88 – 7.74 (m, 3H), 7.49 (dddd, *J* = 18.1, 7.2, 4.6, 2.1 Hz, 5H), 7.38 (dd, *J* = 8.5, 2.2 Hz, 2H), 7.32 (td, *J* = 4.2, 1.7 Hz, 3H), 7.15 (dd, *J* = 8.2, 2.3 Hz, 2H), 5.35 (d, *J* = 3.3 Hz, 1H), 2.33 (d, *J* = 2.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.48, 138.76, 136.78, 133.61, 132.61, 131.90, 129.52, 128.60, 128.42, 128.17, 128.09, 128.07, 127.80, 126.50, 126.36, 126.31, 125.95, 123.72, 90.45, 85.26, 43.67, 21.24.

HRMS calcd for $C_{26}H_{21}$ [M+H], found 333.1635.



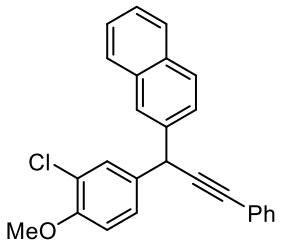
2-(1-(4-(tert-butyl)phenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.21c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.87 – 7.82 (m, 1H), 7.80 (dd, *J* = 8.8, 4.0 Hz, 2H), 7.52 (ddd, *J* = 9.9, 5.9, 2.1 Hz, 3H), 7.46 (ddd, *J* = 7.2, 5.0, 1.7 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.38 – 7.29 (m, 5H), 5.35 (s, 1H), 1.30 (d, *J* = 2.0 Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.96, 139.45, 138.65, 134.00, 133.84, 131.91, 128.57, 128.42, 128.16, 128.10, 127.81, 127.74, 126.57, 126.41, 126.31, 125.95, 125.76, 123.75, 90.52, 85.13, 43.64, 34.63, 31.53.

HRMS calcd for $C_{29}H_{26}$ [M+] 374.2035, found 374.2040.



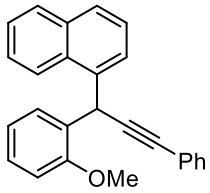
2-(1-(3-chloro-4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.22c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 1.7 Hz, 1H), 7.88 – 7.76 (m, 3H), 7.48 (tdd, *J* = 9.0, 3.9, 1.9 Hz, 6H), 7.38 – 7.29 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.30 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.15, 138.91, 134.91, 133.58, 132.68, 131.91, 129.95, 128.78, 128.47, 128.36, 128.10, 127.84, 127.41, 126.46, 126.41, 126.31, 126.13, 123.43, 122.67, 112.24, 89.73, 85.71, 56.38, 43.00.

HRMS calcd for $C_{26}H_{19}ClONa$ [M+Na] 405.1022, found 405.1041.



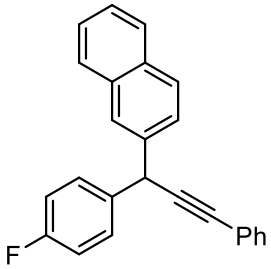
1-(1-(2-methoxyphenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.23c)

White solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.54 – 7.40 (m, 6H), 7.28 – 7.26 (m, 3H), 7.25 – 7.22 (m, 1H), 6.92 (dd, *J* = 9.7, 7.8 Hz, 2H), 6.37 (s, 1H), 3.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.27, 137.40, 134.11, 131.89, 131.37, 129.80, 129.64, 128.82, 128.39, 128.29, 127.93, 127.82, 126.19, 125.90, 125.65, 125.60, 124.11, 123.95, 121.01, 110.98, 90.95, 84.15, 55.89, 33.43.

HRMS calcd for $C_{26}H_{20}ONa$ [M+Na] 371.1412, found 371.1464.



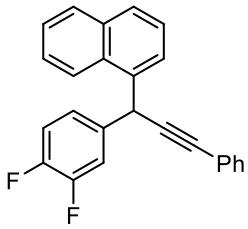
2-(1-(4-fluorophenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.24c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.87 (m, 1H), 7.86 – 7.74 (m, 3H), 7.55 – 7.40 (m, 7H), 7.31 (p, *J* = 3.5 Hz, 3H), 7.06 – 6.96 (m, 2H), 5.35 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.01 (d, *J* = 245.5 Hz), 139.07, 137.43, 133.58, 132.66, 131.89, 129.73 (d, *J* = 8.1 Hz), 128.75, 128.47, 128.34, 128.08, 127.84, 126.44 (d, *J* = 5.3 Hz), 126.33, 126.13, 123.45, 115.63 (d, *J* = 21.3 Hz), 89.95, 85.65, 43.31.

HRMS calcd for $C_{25}H_{17}F$ [M+] 336.1314, found 336.1297.



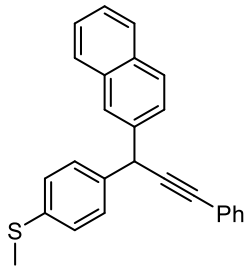
1-(1-(3,4-difluorophenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.25c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 1.8 Hz, 1H), 7.86 – 7.79 (m, 3H), 7.56 – 7.52 (m, 1H), 7.52 – 7.48 (m, 3H), 7.48 – 7.43 (m, 2H), 7.35 – 7.32 (m, 3H), 7.20 (ddt, *J* = 10.3, 3.8, 2.3 Hz, 1H), 7.11 (dt, *J* = 10.2, 8.3 Hz, 1H), 5.33 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 151.01 (dd, *J* = 110.0, 12.8 Hz), 149.04 (dd, *J* = 109.3, 12.9 Hz), 138.75 – 138.60 (m), 138.41, 133.57, 132.72 (d, *J* = 7.2 Hz), 131.90, 128.93, 128.63, 128.52, 128.09, 127.87, 126.57 (d, *J* = 5.9 Hz), 126.30, 126.15, 124.07 (dd, *J* = 6.3, 3.6 Hz), 117.51, 117.37, 117.30, 117.15, 89.18, 86.03, 43.27.

HRMS calcd for $C_{25}H_{20}F_2N$ [M+NH4] 372.1564, found 372.1559.



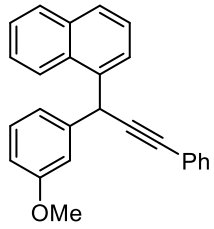
methyl(4-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)phenyl)sulfane (3.26c)

Yellow solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.52 – 7.43 (m, 5H), 7.42 – 7.38 (m, 2H), 7.34 – 7.28 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.34 (s, 1H), 2.46 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.13, 138.66, 137.20, 133.59, 132.65, 131.90, 128.70, 128.68, 128.45, 128.27, 128.09, 127.82, 127.09, 126.42, 126.05, 123.56, 90.04, 85.50, 43.54, 16.13.

HRMS calcd for $C_{26}H_{20}S$ [M+] 364.1286, found 364.1295.



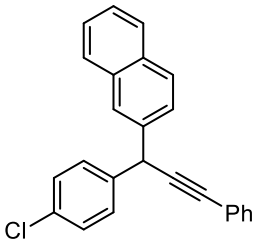
1-(1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.27c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.10 (m, 1H), 7.87 (dt, *J* = 6.8, 2.8 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.52 – 7.39 (m, 5H), 7.31 – 7.27 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.78 (ddd, *J* = 8.3, 2.6, 1.1 Hz, 1H), 5.90 (s, 1H), 3.76 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.92, 142.81, 136.89, 134.32, 131.86, 131.21, 129.69, 128.98, 128.37, 128.29, 128.14, 126.88, 126.31, 125.78, 125.68, 124.33, 123.68, 120.67, 114.35, 112.09, 90.31, 85.44, 55.36, 40.94.

HRMS calcd for $C_{26}H_{20}ONa$ [M+Na] 371.1412, found 371.1866.



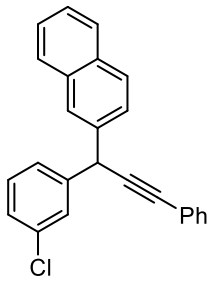
2-(1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.28c)

Yellow solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 7.95 – 7.90 (m, 1H), 7.88 – 7.78 (m, 3H), 7.52 (ddd, *J* = 7.4, 3.3, 1.7 Hz, 3H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.36 – 7.32 (m, 4H), 7.31 (d, *J* = 1.9 Hz, 1H), 5.37 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$)**:** δ 140.22, 138.75, 133.57, 133.01, 132.68, 131.89, 129.57, 128.94, 128.80, 128.48, 128.38, 128.08, 127.84, 126.49, 126.28, 126.17, 123.38, 89.64, 85.79, 43.45.

HRMS calcd for $C_{25}H_{17}ClNa$ [M+Na] 375.0916, found 375.0918.



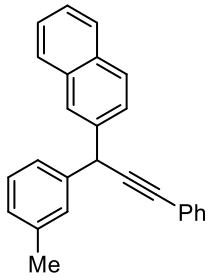
2-(1-(3-chlorophenyl)-3-phenylprop-2-yn-1-yl)naphthalene (3.29c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.8 Hz, 1H), 7.88 – 7.78 (m, 3H), 7.55 – 7.51 (m, 2H), 7.51 – 7.48 (m, 3H), 7.48 – 7.46 (m, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 2.0 Hz, 1H), 5.35 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.68, 138.52, 134.63, 133.58, 132.71, 131.92, 130.05, 128.84, 128.49, 128.41, 128.34, 128.11, 127.84, 127.41, 126.57, 126.50, 126.43, 126.28, 126.20, 123.34, 89.35, 85.92, 43.75.

HRMS calcd for $C_{25}H_{17}ClNa$ [M+Na] 375.0916, found 375.0916.



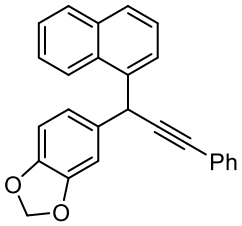
2-(3-phenyl-1-(m-tolyl)prop-2-yn-1-yl)naphthalene (3.30c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 3.0 Hz, 1H), 7.88 – 7.75 (m, 3H), 7.49 (dtd, *J* = 16.1, 5.4, 4.8, 2.6 Hz, 5H), 7.37 – 7.28 (m, 5H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 5.34 (s, 1H), 2.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.60, 139.38, 138.50, 133.61, 132.62, 131.91, 128.92, 128.71, 128.59, 128.42, 128.19, 128.11, 127.95, 127.81, 126.54, 126.40, 126.32, 125.97, 125.28, 123.71, 90.37, 85.33, 44.00, 21.69.

HRMS calcd for $C_{26}H_{20}Li$ [M+Li] 339.1725, found 339.1713.



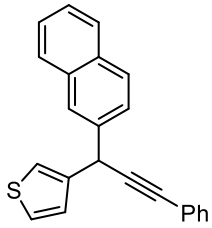
5-(1-(naphthalen-1-yl)-3-phenylprop-2-yn-1-yl)benzo[d][1,3]dioxole (3.31c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 – 8.08 (m, 1H), 7.91 – 7.84 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.54 – 7.40 (m, 5H), 7.32 – 7.27 (m, 3H), 6.97 – 6.88 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.92 (q, *J* = 1.4 Hz, 2H), 5.83 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.99, 146.62, 136.98, 135.20, 134.34, 131.85, 131.11, 129.01, 128.38, 128.34, 128.17, 126.75, 126.31, 125.80, 125.68, 124.30, 123.62, 121.32, 108.80, 108.37, 101.23, 90.44, 85.46, 29.89.

HRMS calcd for $C_{26}H_{18}O_2Na$ [M+Na] 385.1205, found 385.1202.



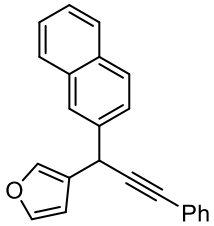
3-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)thiophene (3.35c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 1.8 Hz, 1H), 7.83 (t, *J* = 6.8 Hz, 3H), 7.57 – 7.40 (m, 5H), 7.31 (dd, *J* = 3.7, 2.7 Hz, 3H), 7.27 (s, 2H), 7.08 – 7.03 (m, 1H), 5.41 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.22, 138.69, 133.63, 132.74, 131.90, 128.68, 128.45, 128.27, 128.09, 127.84, 127.72, 126.40, 126.38, 126.32, 126.06, 123.54, 122.01, 89.98, 84.55, 39.72.

HRMS calcd for $C_{23}H_{16}S$ [M+] 324.0973, found 324.0985.



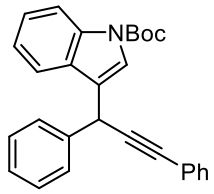
3-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)furan (3.36c)

Yellow liquid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 1.7 Hz, 1H), 7.90 – 7.81 (m, 3H), 7.59 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.51 (qt, *J* = 4.1, 2.0 Hz, 4H), 7.47 (d, *J* = 1.8 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.34 (p, *J* = 3.4 Hz, 3H), 6.38 (d, *J* = 1.8 Hz, 1H), 5.26 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.61, 140.08, 138.27, 133.61, 132.78, 131.90, 128.67, 128.45, 128.28, 128.07, 127.84, 126.60, 126.39, 126.30, 126.29, 126.08, 123.47, 110.51, 89.55, 83.82, 35.19.

HRMS calcd for $C_{23}H_{16}O$ [M+] 308.1201, found 308.1209.



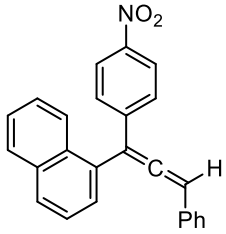
tert-butyl 3-(1,3-diphenylprop-2-yn-1-yl)-1H-indole-1-carboxylate (3.37c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.63 (s, 1H), 7.55 (ddd, *J* = 7.7, 4.8, 1.4 Hz, 3H), 7.48 (dq, *J* = 7.0, 2.3 Hz, 2H), 7.40 – 7.27 (m, 7H), 7.19 (td, *J* = 7.5, 1.1 Hz, 1H), 5.40 (s, 1H), 1.69 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.95, 140.08, 131.85, 130.32, 129.12, 128.80, 128.38, 128.18, 128.06, 127.31, 124.61, 124.08, 123.53, 122.67, 121.32, 120.09, 115.48, 89.37, 84.20, 83.89, 35.51, 28.35.

HRMS calcd for $C_{28}H_{25}NO_2$ [M+] 407.1885, found 407.1882.



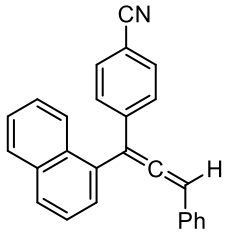
1-(1-(4-nitrophenyl)-3-phenylpropa-1,2-dien-1-yl)naphthalene (3.41c)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.9 Hz, 2H), 7.96 – 7.89 (m, 2H), 7.88 – 7.80 (m, 1H), 7.64 – 7.48 (m, 4H), 7.47 – 7.28 (m, 8H), 6.81 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.29, 146.91, 143.64, 134.17, 132.71, 132.56, 131.80, 129.23, 129.19, 128.82, 128.16, 128.09, 127.69, 127.47, 126.76, 126.38, 125.96, 125.81, 124.13, 110.33, 98.41.

HRMS calcd for $C_{25}H_{17}NO_2Na$ [M+Na] 386.1157, found 386.1158.



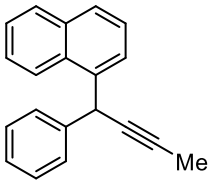
4-(1-(naphthalen-1-yl)-3-phenylpropa-1,2-dien-1-yl)benzonitrile (3.42c)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 5H), 7.46 – 7.38 (m, 3H), 7.35 (d, *J* = 8.2 Hz, 4H), 6.78 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.78, 141.63, 134.14, 132.88, 132.57, 131.84, 129.16, 129.13, 128.77, 128.08, 127.61, 127.42, 126.70, 126.33, 125.94, 125.86, 119.17, 110.72, 110.49, 98.41.

HRMS calcd for $C_{26}H_{18}N$ [M+H] 344.1439, found 344.1440.



1-(1-phenylbut-2-yn-1-yl)naphthalene (3.43c)

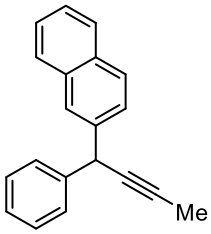
Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 – 7.96 (m, 1H), 7.81 – 7.74 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.55 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 2H), 7.16 – 7.09 (m, 1H), 5.59 (q, *J* = 2.5 Hz, 1H), 1.82 (d, *J* = 2.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.87, 137.64, 134.26, 131.14, 128.93, 128.64, 128.10, 128.05, 126.85, 126.69, 126.17, 125.68, 125.64, 124.37, 81.06, 79.86, 40.38, 4.09.

HRMS calcd for $C_{20}H_{16}Na$ [M+Na] 279.1150, found 279.1165.

S3.29c



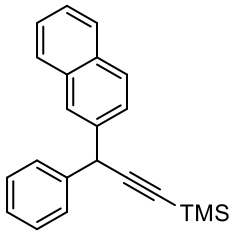
2-(1-phenylbut-2-yn-1-yl)naphthalene (3.44c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 1.8 Hz, 1H), 7.88 – 7.75 (m, 3H), 7.53 – 7.41 (m, 5H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 1H), 5.23 – 5.01 (m, 1H), 1.98 (d, *J* = 2.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.27, 139.85, 133.59, 132.55, 128.70, 128.47, 128.13, 128.05, 127.77, 126.96, 126.54, 126.28, 126.25, 125.87, 81.04, 79.73, 43.56, 4.07.

HRMS calcd for $C_{20}H_{16}Na$ [M+Na] 279.1150, found 279.1158.



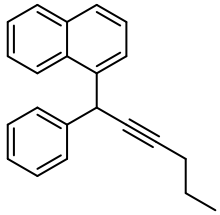
trimethyl(3-(naphthalen-2-yl)-3-phenylprop-1-yn-1-yl)silane (3.45c)

Yellow solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 1.9 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.52 – 7.41 (m, 5H), 7.33 (td, *J* = 8.2, 7.7, 2.0 Hz, 2H), 7.28 – 7.20 (m, 1H), 5.20 (s, 1H), 0.25 (d, *J* = 1.9 Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.40, 139.10, 133.56, 132.59, 128.76, 128.54, 128.14, 128.08, 127.79, 127.08, 126.45, 126.43, 126.31, 125.98, 106.68, 89.73, 44.42, 0.29.

HRMS calcd for $C_{22}H_{22}SiNa$ [M+Na] 337.1388, found 337.1362.



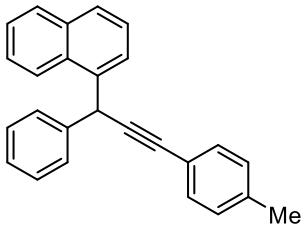
1-(1-phenylhex-2-yn-1-yl)naphthalene (3.46c)

Colorless oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.05 (m, 1H), 7.90 – 7.82 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.50 – 7.42 (m, 3H), 7.42 – 7.36 (m, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.16 (m, 1H), 5.69 (t, *J* = 2.2 Hz, 1H), 2.25 (td, *J* = 7.0, 2.3 Hz, 2H), 1.64 – 1.45 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.96, 137.81, 134.26, 131.17, 128.90, 128.60, 128.10, 128.01, 126.79, 126.68, 126.10, 125.67, 125.64, 124.47, 85.65, 80.93, 40.42, 22.57, 21.20, 13.78.

HRMS calcd for $C_{22}H_{20}Na$ [M+Na] 307.1463, found 307.1477.



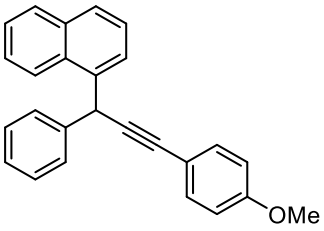
1-(1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)naphthalene (3.47c)

Yellow solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dt, *J* = 7.0, 3.6 Hz, 1H), 7.87 (dt, *J* = 6.7, 3.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.46 (dq, *J* = 6.6, 3.9 Hz, 5H), 7.37 – 7.28 (m, 5H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.92 (s, 1H), 2.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.35, 138.17, 137.18, 134.31, 134.00, 133.84, 131.72, 131.20, 129.12, 128.97, 128.89, 128.72, 128.64, 128.22, 128.19, 126.99, 126.90, 126.27, 125.76, 125.69, 124.39, 120.61, 89.67, 85.50, 40.96, 21.63.

HRMS calcd for $C_{20}H_{16}Na$ [M+Na] 279.1150, found 279.1165.



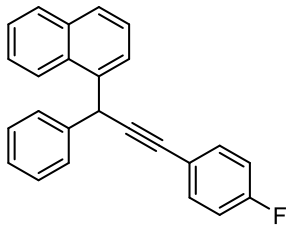
1-(3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-yl)naphthalene (3.48c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (dq, *J* = 6.0, 3.5 Hz, 1H), 7.87 (dt, *J* = 6.0, 3.5 Hz, 1H), 7.81 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.70 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.52 – 7.44 (m, 5H), 7.42 – 7.36 (m, 2H), 7.35 – 7.28 (m, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.92 (s, 1H), 3.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.50, 141.43, 137.26, 134.31, 133.22, 131.20, 128.97, 128.71, 128.63, 128.19, 126.97, 126.88, 126.25, 125.75, 125.69, 124.40, 115.85, 113.97, 88.91, 85.23, 55.46, 40.96.

HRMS calcd for $C_{26}H_{20}ONa$ [M+Na] 371.1412, found 371.1431.



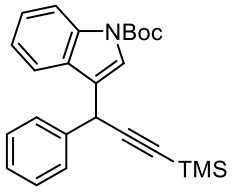
1-(3-(4-fluorophenyl)-1-phenylprop-2-yn-1-yl)naphthalene (3.49c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dt, *J* = 7.0, 3.5 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 6.9 Hz, 1H), 7.53 – 7.38 (m, 7H), 7.36 – 7.28 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 5.91 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.49 (d, *J* = 248.9 Hz), 161.50, 141.09, 136.93, 134.33, 133.69 (d, J = 8.2 Hz), 131.16, 129.02, 128.79, 128.33, 128.16, 127.10, 126.87, 126.33, 125.82, 125.68, 124.30, 115.61 (d, *J* = 22.2 Hz), 90.10, 84.35, 40.89.

HRMS calcd for $C_{25}H_{18}F$ [M+H] 337.1393, found 337.1402.



tert-butyl 3-(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)-1H-indole-1-carboxylate (3.52c)

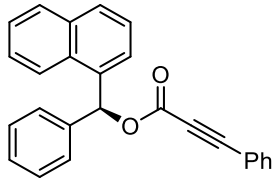
Colorless oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.55 (d, *J* = 1.1 Hz, 1H), 7.48 – 7.38 (m, 3H), 7.35 – 7.27 (m, 3H), 7.26 – 7.21 (m, 1H), 7.17 – 7.09 (m, 1H), 5.16 (s, 1H), 1.67 (s, 9H), 0.19 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.89, 139.89, 128.75, 128.05, 127.25, 124.56, 124.19, 122.55, 121.07, 120.09, 115.43, 105.87, 88.47, 83.78, 35.94, 28.38, 0.23.

HRMS calcd for $C_{25}H_{29}NO_2SiNa$ [M+Na] 426.1865, found 426.1870.

Characterization data for enantioenriched benzyl propiolates:



(*S*)-naphthalen-1-yl(phenyl)methyl 3-phenylpropiolate ((*S*)-3.15b)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

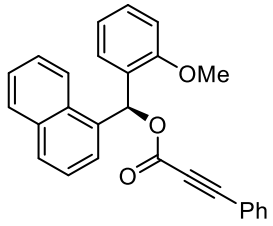
$[\alpha]_D^{25}$ = +83.3 (*c* .00156, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 – 7.95 (m, 1H), 7.87 (s, 2H), 7.75 (s, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.54 – 7.51 (m, 1H), 7.50 – 7.46 (m, 2H), 7.43 (dd, *J* = 6.6, 1.4 Hz, 3H), 7.39 – 7.33 (m, 4H), 7.33 – 7.31 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.45, 138.98, 134.55, 134.07, 133.25, 130.90, 130.76, 129.36, 129.02, 128.81, 128.74, 128.51, 127.84, 126.74, 126.00, 125.84, 125.41, 123.94, 119.73, 87.31, 80.81, 76.28.

HRMS calcd for $C_{26}H_{18}O_2Na$ [M+Na] 385.1205, found 385.1206.

HPLC analysis: 94% ee (Chiralcel OD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 17.3 min, minor R_t = 23.8 min).



(*S*)-(2-methoxyphenyl)(naphthalen-1-yl)methyl 3-phenylpropiolate ((*S*)-3.23b)

White solid isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

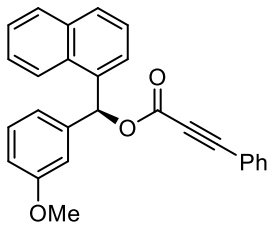
$[\alpha]_D^{25}$ = -113.1 (*c* .0024, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 8.05 – 7.95 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.54 (m, 3H), 7.52 – 7.46 (m, 3H), 7.46 – 7.40 (m, 1H), 7.39 – 7.28 (m, 3H), 7.22 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.90 (d, *J* = 1.1 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.08, 153.31, 134.78, 133.92, 133.25, 131.00, 130.79, 129.97, 128.99, 128.92, 128.86, 128.71, 127.10, 126.60, 125.93, 125.40, 124.98, 123.88, 120.75, 119.87, 110.91, 86.82, 81.00, 70.59, 55.86.

HRMS calcd for $C_{27}H_{20}O_3Na$ [M+Na] 415.1310, found 415.1314.

HPLC analysis: 69% ee (Chiralcel OD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 20.1 min, major R_t = 29.8 min).



(*S*)-(3-methoxyphenyl)(naphthalen-1-yl)methyl 3-phenylpropiolate ((*S*)-3.27b)

Colorless oil isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

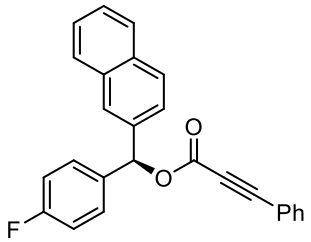
$[\alpha]_D^{25}$ = +27.5 (*c* .0004, DCM)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 – 7.99 (m, 1H), 7.92 – 7.83 (m, 2H), 7.73 (s, 1H), 7.65 (s, 1H), 7.63 – 7.56 (m, 2H), 7.56 – 7.48 (m, 3H), 7.47 – 7.41 (m, 1H), 7.37 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.86 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.89, 153.41, 140.53, 134.43, 134.04, 133.22, 130.89, 130.79, 129.85, 129.39, 129.00, 128.72, 126.74, 125.99, 125.90, 125.38, 123.87, 120.14, 119.68, 113.72, 113.62, 87.34, 80.78, 76.07, 55.39.

HRMS calcd for $C_{27}H_{20}O_3Na$ [M+Na] 415.1310, found 415.1314.

HPLC analysis: 97% ee (Chiralcel OD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 24.0 min, minor R_t = 75.1 min).



(*S*)-(4-fluorophenyl)(naphthalen-2-yl)methyl 3-phenylpropiolate ((*S*)-3.24b)

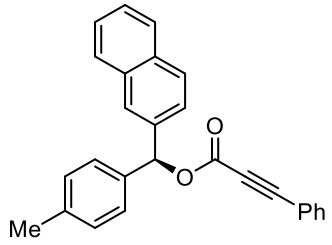
Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.80 (m, 4H), 7.66 – 7.58 (m, 2H), 7.54 – 7.48 (m, 2H), 7.48 – 7.35 (m, 6H), 7.16 (s, 1H), 7.06 (t, *J* = 8.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.73 (d, J = 247.3 Hz), 153.33, 136.54, 135.29 (d, J = 3.4 Hz), 133.25, 130.98, 129.51 (d, *J* = 8.2 Hz), 129.47, 128.80, 128.78, 128.37, 127.89, 126.67, 126.34, 124.91, 119.65, 115.75 (d, J = 21.7 Hz), 87.43, 80.72, 78.15.

HRMS calcd for $C_{26}H_{18}FO_2$ [M+H] 381.1291, found 381.1281.

HPLC analysis: 94% ee (Chiralcel OD, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 25.6 min, major R_t = 30.0 min).



(*S*)-naphthalen-2-yl(*p*-tolyl)methyl 3-phenylpropiolate ((*S*)-3.20b)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

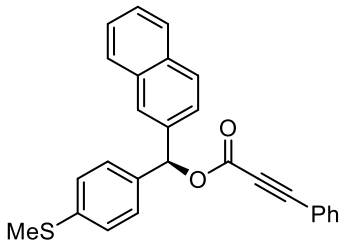
$[\alpha]_D^{25}$ = +46.2 (*c* .00026, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 1.6 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 3H), 7.60 (s, 2H), 7.52 – 7.42 (m, 4H), 7.41 – 7.29 (m, 4H), 7.21 – 7.12 (m, 3H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.47, 138.32, 136.97, 136.46, 133.27, 133.24, 133.19, 130.87, 129.49, 128.75, 128.65, 128.38, 127.86, 127.62, 126.52, 126.50, 126.26, 125.09, 119.80, 87.12, 80.91, 78.80, 21.37.

HRMS calcd for $C_{27}H_{20}O_2Na$ [M+Na] 399.1361, found 399.1372.

HPLC analysis: 85% ee (Chiralcel OD, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 20.1 min, major R_t = 60.6 min).



(*S*)-(4-(methylthio)phenyl)(naphthalen-2-yl)methyl 3-phenylpropiolate ((*S*)-3.26b)

White solid isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

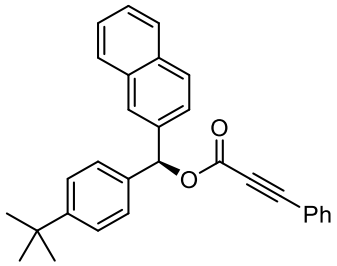
$[\alpha]_D^{25}$ = +30.5 (*c* .00072, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 – 7.87 (m, 1H), 7.83 (d, *J* = 8.6 Hz, 3H), 7.61 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.49 (s, 2H), 7.47 – 7.42 (m, 2H), 7.41 – 7.33 (m, 4H), 7.26 – 7.23 (m, 2H), 7.13 (s, 1H), 2.47 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.40, 139.06, 136.65, 136.13, 133.25, 130.93, 128.77, 128.72, 128.38, 128.19, 127.88, 126.66, 126.60, 126.34, 125.03, 119.73, 87.29, 80.80, 78.51, 15.83.

HRMS calcd for $C_{27}H_{20}O_2SNa$ [M+Na] 431.1082, found 431.1079.

HPLC analysis: 62% ee (Chiralcel OD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 76.1 min, major R_t = 87.8 min).



(*S*)-(4-(tert-butyl)phenyl)(naphthalen-2-yl)methyl 3-phenylpropiolate ((*S*)-3.21b)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

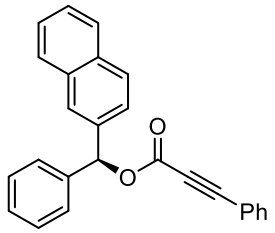
$[\alpha]_D^{25}$ = +45.2 (*c* .0013, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.90 (m, 1H), 7.84 (d, *J* = 8.6 Hz, 3H), 7.65 – 7.57 (m, 2H), 7.52 – 7.47 (m, 3H), 7.46 (s, 1H), 7.41 – 7.33 (m, 6H), 7.16 (s, 1H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.47, 151.44, 136.94, 136.36, 133.28, 133.23, 133.20, 130.86, 128.75, 128.63, 128.38, 127.86, 127.40, 126.50, 126.48, 126.23, 125.74, 125.09, 119.80, 87.10, 80.93, 78.80, 34.77, 31.47.

HRMS calcd for $C_{30}H_{26}O_2Na$ [M+Na] 441.1831, found 441.1838.

HPLC analysis: 94% ee (Chiralpak AD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 21.7 min, major R_t = 22.6 min).



(*S*)-naphthalen-2-yl(phenyl)methyl 3-phenylpropiolate ((*S*)-3.17b)

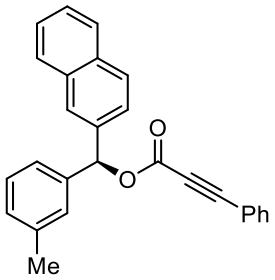
White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 1.7 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 3H), 7.64 – 7.59 (m, 2H), 7.48 (ddt, *J* = 18.9, 7.5, 2.6 Hz, 6H), 7.38 (t, *J* = 7.6 Hz, 4H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.19 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.41, 139.37, 136.79, 133.24, 130.90, 128.80, 128.75, 128.70, 128.44, 128.38, 127.86, 127.54, 126.56, 126.47, 125.11, 119.73, 87.24, 80.84, 78.85.

HRMS calcd for $C_{26}H_{18}O_2Li$ [M+Li] 369.1467, found 369.1474.

HPLC analysis: 92% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 14.8 min, major R_t = 20.1 min).



(*S*)-naphthalen-2-yl(*m*-tolyl)methyl 3-phenylpropiolate ((*S*)-3.30b)

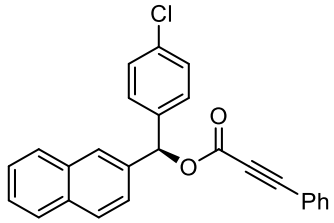
Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 1.6 Hz, 1H), 7.82 (m, 3H), 7.66 – 7.57 (m, 2H), 7.53 – 7.41 (m, 4H), 7.41 – 7.33 (m, 2H), 7.25 (d, *J* = 3.5 Hz, 3H), 7.14 (s, 2H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.44, 139.29, 138.55, 136.91, 133.25, 133.21, 130.89, 129.25, 128.76, 128.70, 128.67, 128.40, 128.21, 127.87, 126.53, 126.37, 125.13, 124.65, 124.63, 119.79, 87.18, 80.90, 78.93, 21.67.

HRMS calcd for $C_{27}H_{20}O_2Na$ [M+Na] 399.1361, found 399.1362.

HPLC analysis: 94% ee (Chiralcel OD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 16.2 min, major R_t = 22.3 min).



(*R*)-(4-chlorophenyl)(naphthalen-2-yl)methyl 3-phenylpropiolate ((*R*)-3.28b)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

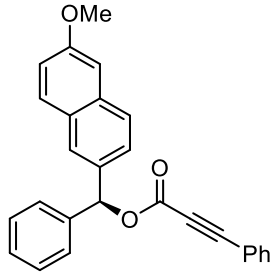
$[\alpha]_D^{25}$ = -16.9 (*c* .001, DCM)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 1.7 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 3H), 7.65 – 7.58 (m, 2H), 7.54 – 7.48 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.37 (m, 4H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.14 (s, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.27, 137.95, 136.30, 134.36, 133.28, 133.26, 133.22, 131.00, 129.01, 128.94, 128.86, 128.78, 128.38, 127.89, 126.73, 126.69, 126.54, 124.92, 119.62, 87.53, 80.66, 78.11.

HRMS calcd for $C_{26}H_{16}ClO_2$ [M-H] 395.0839, found 395.0832.

HPLC analysis: 91% ee (Chiralcel OD, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 20.8 min, minor R_t = 33.1 min).



(*S*)-(6-methoxynaphthalen-2-yl)(phenyl)methyl 3-phenylpropiolate ((*S*)-3.18b)

White solid isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

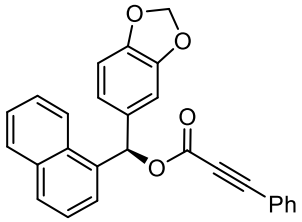
$[\alpha]_D^{25}$ = +43.7 (*c* .006, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.7, 6.8 Hz, 2H), 7.64 – 7.59 (m, 2H), 7.45 (td, *J* = 7.1, 1.7 Hz, 4H), 7.38 (ddd, *J* = 8.5, 5.3, 2.0 Hz, 4H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.13 (d, *J* = 2.5 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.24, 153.44, 139.52, 134.52, 134.47, 133.21, 130.86, 129.85, 128.76, 128.73, 128.66, 128.33, 127.50, 127.44, 126.52, 125.77, 119.75, 119.35, 105.81, 87.13, 80.88, 78.91, 55.49.

HRMS calcd for $C_{27}H_{20}O_3Na$ [M+Na] 415.1310, found 415.1306.

HPLC analysis: 81% ee (Chiralcel OD-H, 99:1 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 46.1 min, major R_t = 58.9 min).



(*R*)-benzo[d][1,3]dioxol-5-yl(naphthalen-1-yl)methyl 3-phenylpropiolate ((*R*)-3.31b)

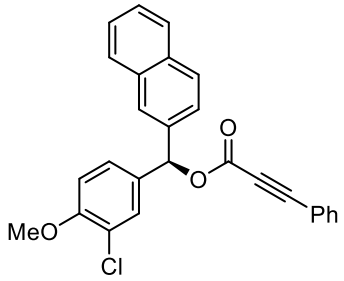
Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 – 7.91 (m, 1H), 7.91 – 7.83 (m, 2H), 7.70 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.65 (s, 1H), 7.59 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.52 (d, *J* = 1.0 Hz, 1H), 7.48 (d, *J* = 9.6 Hz, 3H), 7.38 (d, *J* = 7.8 Hz, 2H), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.94 (dd, *J* = 7.4, 1.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.38, 148.08, 147.88, 134.48, 134.05, 133.26, 132.85, 130.91, 130.53, 129.27, 129.03, 128.75, 126.71, 126.00, 125.40, 125.10, 123.84, 122.09, 119.73, 108.63, 108.48, 101.44, 87.31, 80.81, 76.10.

HRMS calcd for $C_{27}H_{18}O_4Na$ [M+Na] 429.1103, found 429.1107.

HPLC analysis: This substrate could not be separated in HPLC.



(*R*)-(3-chloro-4-methoxyphenyl)(naphthalen-2-yl)methyl 3-phenylpropiolate ((*R*)-3.23b)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

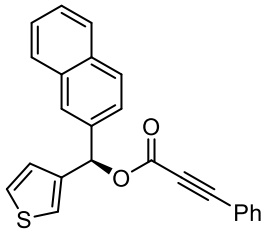
$[\alpha]_D^{25}$ = +25.8 (*c* .0013, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 – 7.80 (m, 4H), 7.65 – 7.58 (m, 2H), 7.54 – 7.47 (m, 2H), 7.46 (q, *J* = 2.6 Hz, 2H), 7.43 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.30 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.09 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.13, 153.31, 136.41, 133.27, 133.24, 132.62, 130.97, 129.63, 128.82, 128.78, 128.39, 127.89, 127.37, 126.66, 126.21, 124.85, 122.87, 119.67, 112.06, 87.46, 80.72, 77.88, 56.39.

HPLC analysis: 42% ee (Chiralpak AD-H, 96:4 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 57.4 min, minor R_t = 46.4 min).

HRMS calcd for $C_{27}H_{19}ClO_3Na$ [M+Na] 449.0920, found 449.0935.



(*R*)-naphthalen-2-yl(thiophen-3-yl)methyl 3-phenylpropiolate ((*R*)-3.35b)

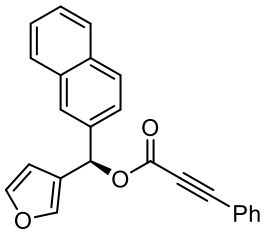
Yellow oil isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.6 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 3H), 7.65 – 7.56 (m, 2H), 7.55 – 7.48 (m, 3H), 7.46 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 5.0 Hz, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.23 (s, 1H), 7.08 (dd, *J* = 5.0, 1.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.42, 140.50, 136.39, 133.36, 133.26, 133.24, 130.92, 128.76, 128.71, 128.40, 127.90, 127.02, 126.63, 126.61, 126.59, 126.47, 125.04, 123.98, 119.72, 87.28, 80.79, 75.30.

HRMS calcd for $C_{24}H_{16}O_3Na$ [M+Na] 375.0997 found 375.0999.

HPLC analysis**:** 72% ee (Chiralpak AD-H, 96:4 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 36.8 min, major R_t = 39.9 min).



(*R*)-furan-3-yl(naphthalen-2-yl)methyl 3-phenylpropiolate ((*R*)-3.36b)

White solid isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

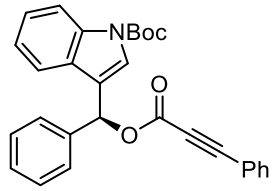
$[\alpha]_D^{25}$ = +115.4 (*c* .00078, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 1.7 Hz, 1H), 7.92 – 7.81 (m, 3H), 7.64 – 7.57 (m, 2H), 7.55 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.48 – 7.43 (m, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.40 – 7.35 (m, 3H), 7.12 (s, 1H), 6.45 – 6.39 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.45, 143.81, 141.53, 135.89, 133.40, 133.23, 130.92, 128.76, 128.70, 128.39, 127.90, 126.65, 126.60, 126.39, 124.92, 119.70, 109.92, 80.75, 72.39.

HRMS calcd for $C_{24}H_{16}O_3Na$ [M+Na] 375.0997, found 375.0984.

HPLC analysis: 75% ee (Chiralpak AD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 30.6 min, major R_t = 36.7 min).



***t*-butyl (*S*)-3-(phenyl((3-phenylpropioloyl)oxy)methyl)-1H-indole-1-carboxylate ((*S*)-3.37b)**

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

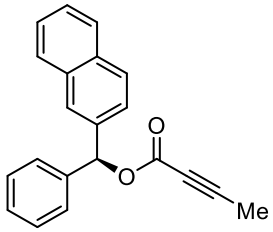
$[\alpha]_D^{25}$ = -28 (*c* .0013, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.54 – 7.49 (m, 2H), 7.48 – 7.42 (m, 2H), 7.38 (ddd, *J* = 8.0, 3.4, 1.4 Hz, 3H), 7.36 – 7.32 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 7.21 (q, *J* = 7.6, 6.4 Hz, 1H), 1.67 (d, *J* = 1.4 Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.52, 149.81, 138.19, 135.92, 133.25, 132.84, 130.89, 128.81, 128.74, 128.68, 127.44, 125.41, 124.93, 123.05, 120.16, 119.73, 119.34, 115.55, 87.26, 84.33, 80.72, 72.88, 28.35.

HRMS calcd for $C_{29}H_{25}NO_4Na$ [M+Na] 474.1681, found 474.1683.

HPLC analysis: 87% ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 17.6 min, minor R_t = 25.2 min).



(*S*)-naphthalen-2-yl(phenyl)methyl but-2-ynoate ((*S*)-3.44b)

White solid isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

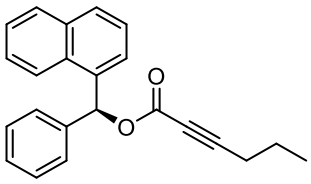
$[\alpha]_D^{25}$ = +28.8 (*c* .0029, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.77 (m, 4H), 7.52 – 7.45 (m, 2H), 7.45 – 7.38 (m, 3H), 7.35 (s, 2H), 7.33 – 7.27 (m, 1H), 7.09 (s, 1H), 2.01 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.04, 139.45, 136.87, 133.23, 133.19, 128.77, 128.66, 128.36, 127.85, 127.46, 126.52, 126.35, 125.05, 86.63, 78.54, 72.64, 4.13.

HRMS calcd for $C_{21}H_{16}O_2Li$ [M+Li] 307.1310, found 307.1305.

HPLC analysis: 92% ee (Chiralpak AD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 21.8 min, major R_t = 23.9 min).



(*S*)-naphthalen-1-yl(phenyl)methyl hex-2-ynoate ((*S*)-3.46b)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

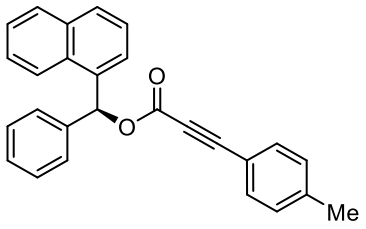
$[\alpha]_D^{25}$ = +28.2 (*c* .00078, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 0.75, 129.26, 128.97, 128.74, 128.39, 127.77, 126.66, 125.95, 125.79, 125.37, 123.96, 90.68, 75.92, 73.35, 21.21, 20.90, 13.70.

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.22, 139.10, 134.67, 134.05, 130.75, 129.26, 128.97, 128.74, 128.39, 127.77, 126.66, 125.95, 125.79, 125.37, 123.96, 90.68, 75.92, 73.35, 21.21, 20.90, 13.70.

HRMS calcd for $C_{23}H_{20}O_2Li$ [M+Li] 335.1623, found 335.1644.

HPLC analysis: 93% ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 19.3 min, minor R_t = 20.5 min).



(*S*)-naphthalen-1-yl(phenyl)methyl 3-(*p*-tolyl) ((*S*)-3.47b)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

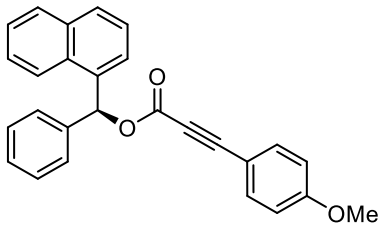
$[\alpha]_D^{25}$ = +78.7 (*c* .0028, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 – 7.95 (m, 1H), 7.87 (t, *J* = 7.4 Hz, 2H), 7.74 (s, 1H), 7.66 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.50 – 7.45 (m, 4H), 7.44 – 7.40 (m, 2H), 7.34 (dt, *J* = 14.2, 7.0 Hz, 3H), 7.17 (d, *J* = 8.1 Hz, 2H), 2.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.58, 141.58, 139.05, 134.62, 134.07, 133.26, 130.78, 129.54, 129.32, 129.00, 128.79, 128.48, 127.85, 126.72, 125.99, 125.84, 125.41, 123.97, 116.61, 87.88, 80.50, 76.15, 21.93.

HRMS calcd for $C_{27}H_{20}O_2$ [M+] 376.1463, found 376.1453.

HPLC analysis: 91% ee (Chiralcel OD-H, 97:3 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 16.7 min, minor R_t = 21.3 min).



(*S*)-naphthalen-1-yl(phenyl)methyl3-(4-methoxyphenyl)propiolate ((*S*)-3.48b)

White solid isolated from flash chromatography using: 19:1 hexanes:EtOAc as eluent.

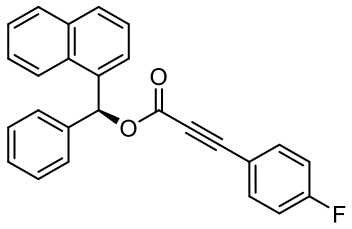
$[\alpha]_D^{25}$ = +78.1 (*c* .0092, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 – 7.97 (m, 1H), 7.92 – 7.82 (m, 2H), 7.74 (s, 1H), 7.65 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.58 – 7.45 (m, 5H), 7.45 – 7.39 (m, 2H), 7.38 – 7.27 (m, 3H), 6.93 – 6.81 (m, 2H), 3.83 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.74, 153.71, 139.10, 135.23, 134.67, 134.06, 130.79, 129.30, 128.99, 128.78, 128.45, 127.85, 126.70, 125.98, 125.83, 125.41, 123.97, 114.45, 111.50, 88.21, 80.31, 76.05, 55.58.

HRMS calcd for $C_{27}H_{20}O_3Na$ [M+Na] 415.1310, found 415.1308.

HPLC analysis: 86% ee (Chiralcel OD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 33.5 min, minor R_t = 45.0 min).



(*S*)-naphthalen-1-yl(phenyl)methyl 3-(4-fluorophenyl)propiolate ((*S*)-3.49b)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

$[\alpha]_D^{25}$ = +60.3 (*c* .006, DCM).

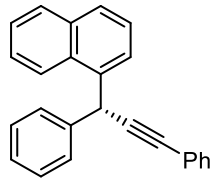
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 – 7.95 (m, 1H), 7.88 (ddt, *J* = 7.9, 5.6, 3.0 Hz, 2H), 7.74 (s, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.59 (ddd, *J* = 8.9, 5.1, 2.4 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.42 (dt, *J* = 5.8, 1.6 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.07 (td, *J* = 9.0, 2.3 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.13 (d, *J* = 253.5 Hz), 153.34, 138.92, 135.53 (d, *J* = 8.9 Hz), 134.49, 134.07, 130.75, 129.39, 129.03, 128.82, 128.54, 127.83, 126.75, 126.02, 125.84, 125.40, 123.91, 116.31 (d, *J* = 22.6 Hz), 115.85 (d, *J* = 3.5 Hz), 86.24, 80.72, 76.33.

HRMS calcd for $C_{26}H_{21}FO_2N$ [M+NH_4] 398.1556, found 398.1548.

HPLC analysis: 91% ee (Chiralcel OD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 25.0 min, minor R_t = 34.5 min).

Characterization data for enantioenriched benzyl alkynes:



(*R*)-1-(1,3-diphenylprop-2-yn-1-yl)naphthalene ((*R*)-3.15c)

Yellow solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

$[\alpha]_D^{25}$ = +30.4 (*c* .00046, DCM).

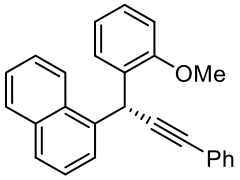
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.07 (m, 1H), 7.85 (dd, *J* = 6.3, 3.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 1.1 Hz, 1H), 7.44 (td, *J* = 6.8, 3.4 Hz, 7H), 7.33 – 7.24 (m, 5H), 7.22 (d, *J* = 4.6 Hz, 1H), 5.91 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.21, 137.04, 134.32, 131.86, 131.19, 128.99, 128.75, 128.37, 128.28, 128.19, 128.14, 127.04, 126.91, 126.30, 125.79, 125.69, 124.36, 123.69, 90.45, 85.44, 40.95.

HRMS calcd for $C_{25}H_{18}Li$ [M+Li] 325.1569, found 325.1578.

HPLC analysis: 88% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 10.2 min, major R_t = 11.7 min).

S3.8c′



(*R*)-1-(1-(2-methoxyphenyl)-3-phenylprop-2-yn-1-yl)naphthalene ((*R*)-3.23c)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

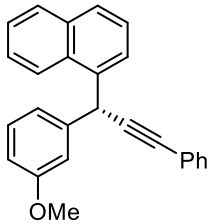
$[\alpha]_D^{25}$ = +46.2 (*c* .00026, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.92 – 7.82 (m, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.46 (dddd, *J* = 14.4, 12.5, 6.4, 1.6 Hz, 6H), 7.27 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.25 – 7.22 (m, 1H), 6.98 – 6.87 (m, 2H), 6.37 (s, 1H), 3.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.27, 137.40, 134.11, 131.89, 131.37, 129.80, 129.64, 128.82, 128.29, 127.93, 127.82, 126.19, 125.90, 125.65, 125.60, 124.11, 123.95, 121.01, 110.98, 90.95, 84.15, 55.89, 33.43.

HRMS calcd for $C_{26}H_{20}ONa$ [M+Na] 371.1412, found 371.1406.

HPLC analysis: 64% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 54.7 min, minor R_t = 58.1 min).



(*R*)-1-(1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-yl)naphthalene ((*R*)-3.27c)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

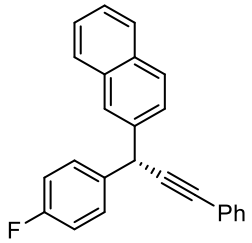
$[\alpha]_D^{25}$ = -40.4 (*c* .00052, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.94 – 7.84 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.70 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.55 – 7.38 (m, 5H), 7.28 (td, *J* = 3.3, 1.6 Hz, 3H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.13 – 6.98 (m, 2H), 6.82 – 6.70 (m, 1H), 5.90 (s, 1H), 3.76 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.92, 142.81, 136.89, 134.32, 131.86, 131.21, 129.69, 128.98, 128.37, 128.29, 128.14, 126.88, 126.31, 125.78, 125.68, 124.33, 123.68, 120.67, 114.35, 112.09, 90.31, 85.44, 55.36, 40.94.

HRMS calcd for $C_{26}H_{20}ONa$ [M+Na] 371.1412, found 371.1411.

HPLC analysis: 96% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 49.4 min, minor R_t = 59.1 min).



(*R*)-2-(1-(4-fluorophenyl)-3-phenylprop-2-yn-1-yl)naphthalene ((*R*)-3.24c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

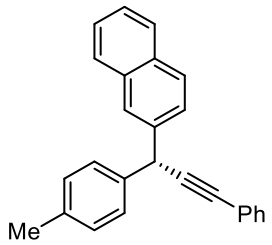
$[\alpha]_D^{25}$ = -23.1 (*c* .0011, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.88 (m, 1H), 7.87 – 7.75 (m, 3H), 7.55 – 7.39 (m, 7H), 7.37 – 7.29 (m, 3H), 7.09 – 6.95 (m, 2H), 5.37 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.01 (d, *J* = 245.7 Hz), 139.07, 137.44 (d, *J* = 2.9 Hz), 133.58, 132.66, 131.89, 129.73 (d, *J* = 8.1 Hz), 128.75, 128.47, 128.34, 128.08, 127.84, 126.46, 126.42, 126.33, 126.13, 123.45, 115.63 (d, J = 21.1 Hz), 89.95, 85.65, 43.31.

HRMS calcd for $C_{25}H_{17}FNa$ [M+Na] – 359.1212, found 359.1214.

HPLC analysis: 96% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 41.1 min, minor R_t = 44.4 min).



(*R*)-2-(3-phenyl-1-(p-tolyl)prop-2-yn-1-yl)naphthalene ((*R*)-3.20c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

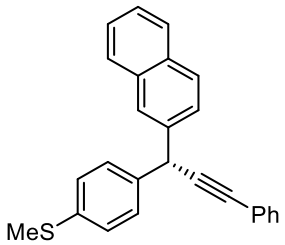
$[\alpha]_D^{25}$ = +6.3 (*c* .00254, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.7 Hz, 1H), 7.87 – 7.73 (m, 3H), 7.50 (dd, *J* = 5.7, 2.2 Hz, 3H), 7.48 – 7.44 (m, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.32 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.35 (s, 1H), 2.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.48, 138.76, 136.79, 133.61, 132.61, 131.90, 129.52, 128.60, 128.42, 128.17, 128.09, 128.07, 127.80, 126.50, 126.36, 126.31, 125.95, 123.72, 90.44, 85.26, 43.67, 21.24.

HRMS calcd for $C_{26}H_{20}Na$ [M+Na] 355.1463, found 355.1457.

HPLC analysis : 96% ee (Chiralcel OD, 99.6:0.4 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 26.7 min, minor R_t = 28.4 min).



(*R*)-methyl(4-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)phenyl)sulfane ((*R*)-3.26c)

Yellow solid isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

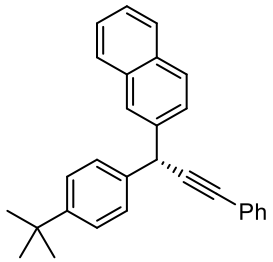
$[\alpha]_D^{25}$ = -23.4 (*c* .00064, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 1.6 Hz, 1H), 7.80 (m, 3H), 7.53 – 7.48 (m, 3H), 7.47 (d, *J* = 2.3 Hz, 2H), 7.43 – 7.38 (m, 2H), 7.34 – 7.30 (m, 3H), 7.25 – 7.20 (m, 2H), 5.34 (s, 1H), 2.47 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.12, 138.65, 137.20, 133.59, 132.64, 131.89, 128.69, 128.67, 128.45, 128.27, 128.08, 127.82, 127.08, 126.41, 126.05, 123.56, 90.04, 85.49, 43.53, 16.12.

HRMS for $C_{26}H_{19}S$ [M-H] 363.1207, found 363.1209.

HPLC analysis: 96% ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 26.2 min, minor R_t = 30.5 min).



(*R*)-2-(1-(4-(tert-butyl)phenyl)-3-phenylprop-2-yn-1-yl)naphthalene ((*R*)-3.21c)

Colorless oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

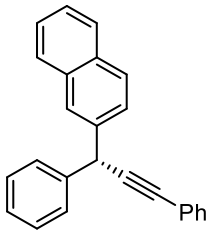
$[\alpha]_D^{25}$ = -291.7 (*c* .00012, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 1.7 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.56 – 7.49 (m, 3H), 7.46 (s, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36 (s, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.32 (dd, *J* = 5.1, 1.8 Hz, 3H), 5.36 (s, 1H), 1.30 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.96, 139.45, 138.65, 133.63, 132.62, 131.91, 128.57, 128.42, 128.16, 128.09, 127.81, 127.74, 126.57, 126.41, 126.31, 125.95, 125.76, 123.74, 90.52, 85.14, 43.64, 31.53.

HRMS calcd for $C_{29}H_{26}Na$ [M+Na] 397.1932, found 397.1931.

HPLC analysis: 96% ee (Chiralpak AD-H, 99.7:0.3 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 27.8 min, minor R_t = 26.0 min).



(*R*)-2-(1,3-diphenylprop-2-yn-1-yl)naphthalene ((*R*)-3.17c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

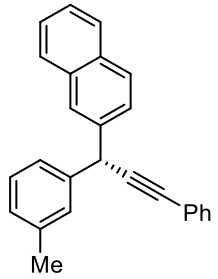
$[\alpha]_D^{25}$ = -44.4 (*c* .00018, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 1.6 Hz, 1H), 7.85 – 7.74 (m, 3H), 7.49 (ddd, *J* = 7.0, 4.0, 1.8 Hz, 5H), 7.45 (s, 1H), 7.36 – 7.27 (m, 5H), 7.24 (d, *J* = 7.0 Hz, 2H), 5.37 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) **:** δ 141.68, 139.29, 133.61, 132.64, 131.91, 128.83, 128.63, 128.44, 128.21, 128.10, 127.81, 127.16, 126.51, 126.46, 126.36, 126.01, 123.64, 90.22, 85.43, 44.06.

HRMS calcd for $C_{25}H_{17}$ [M-H] 317.1330, found 317.1328.

HPLC analysis**:** 89% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 9.5 min, minor R_t = 10.1 min).



(*R*)-2-(3-phenyl-1-(m-tolyl)prop-2-yn-1-yl)naphthalene ((*R*)-3.30c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

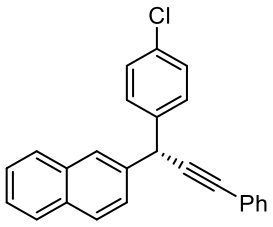
$[\alpha]_D^{25}$ = -8.3 (*c* .00084, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.80 (m, 3H), 7.51 (tt, *J* = 4.9, 2.6 Hz, 3H), 7.46 (ddd, *J* = 7.3, 5.0, 1.9 Hz, 2H), 7.31 (dd, *J* = 9.0, 6.5 Hz, 5H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 5.34 (s, 1H), 2.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.60, 139.38, 138.50, 133.61, 132.69, 132.62, 131.91, 128.92, 128.71, 128.59, 128.42, 128.19, 128.11, 127.95, 127.81, 126.54, 126.40, 126.32, 125.97, 125.28, 123.71, 90.37, 85.33, 44.00, 21.69.

HRMS for $C_{26}H_{19}$ [M-H] 331.1487, found 331.1488.

HPLC analysis: 91% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 28.6 min, minor R_t = 32.3 min).



(*S*)-2-(1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl)naphthalene ((*S*)-3.28c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

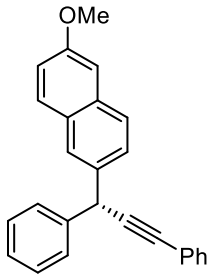
$[\alpha]_D^{25}$ = -84.6 (*c* .00026, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.86 – 7.76 (m, 3H), 7.53 – 7.45 (m, 5H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.32 (q, *J* = 2.8, 2.1 Hz, 4H), 7.30 – 7.27 (m, 1H), 5.35 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.22, 138.75, 133.57, 133.01, 132.68, 131.89, 129.57, 128.94, 128.80, 128.38, 128.08, 127.84, 126.49, 126.28, 126.17, 123.38, 89.64, 85.79, 43.45.

HRMS for $C_{25}H_{16}Cl$ [M-H] 351.0941, found 351.0940.

HPLC analysis: 96% ee (Chiralpak AD-H, 99.6:0.4 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 82.2 min, minor R_t = 95.6 min).



(*R*)-2-(1,3-diphenylprop-2-yn-1-yl)-6-methoxynaphthalene ((*R*)-3.18c)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

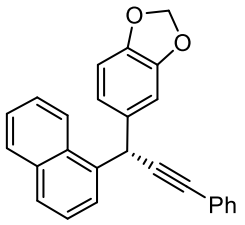
$[\alpha]_D^{25}$ = -127.3 (*c* .00022, DCM)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.43 (m, 5H), 7.37 – 7.28 (m, 5H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.17 – 7.07 (m, 2H), 5.35 (s, 1H), 3.90 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.83, 141.89, 137.02, 133.73, 131.90, 129.56, 129.03, 128.79, 128.42, 128.18, 127.48, 127.09, 127.00, 126.30, 123.69, 119.11, 105.83, 90.43, 85.27, 55.49, 43.87.

HRMS calcd for $C_{26}H_{19}O$ [M-H] 347.1436, found 347.1434.

HPLC analysis: 96% ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 25.1 min, minor R_t = 20.5 min).



(*S*)-5-(1-(naphthalen-1-yl)-3-phenylprop-2-yn-1-yl)benzo[d][1,3]dioxole ((*S*)-3.31c)

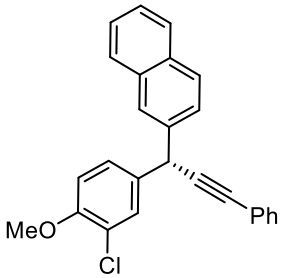
Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.07 (m, 1H), 7.91 – 7.85 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.38 (m, 5H), 7.31 – 7.27 (m, 3H), 6.94 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 5.92 (q, *J* = 1.4 Hz, 2H), 5.84 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.99, 146.62, 136.98, 135.20, 134.34, 131.85, 131.11, 129.01, 128.38, 128.34, 128.17, 126.75, 126.31, 125.80, 125.68, 124.30, 123.62, 121.32, 108.80, 108.37, 101.23, 90.44, 85.46, 29.89.

HPLC analysis: 27% ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 21.9 min, minor R_t = 27.0 min).

HRMS calcd for $C_{26}H_{18}O_2Na$ [M+Na] 385.1205, found 385.1207.



(*S*)-2-(1-(3-chloro-4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)naphthalene ((*S*)-3.22c)

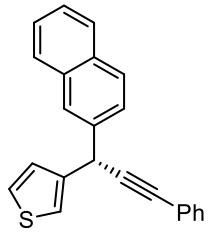
Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.87 – 7.77 (m, 3H), 7.56 – 7.41 (m, 6H), 7.39 – 7.29 (m, 4H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.30 (d, *J* = 1.9 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.15, 138.91, 134.91, 133.58, 132.68, 131.91, 129.95, 128.78, 128.47, 128.36, 128.10, 127.84, 127.41, 126.46, 126.41, 126.31, 126.13, 123.43, 122.67, 112.24, 89.73, 85.71, 56.38, 43.00.

HPLC analysis: 63% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 45.9 min, minor R_t = 38.4 min).

HRMS calcd for $C_{26}H_{19}ClO$ [M+] 382.1124, found 381.1125.



(*S*)-3-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)thiophene ((*S*)-3.35c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

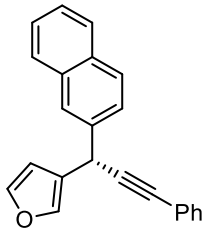
$[\alpha]_D^{25}$ = -37.5 (*c* .00032, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 1.8 Hz, 1H), 7.83 (s, 2H), 7.81 (d, *J* = 3.2 Hz, 1H), 7.54 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.50 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.47 – 7.43 (m, 1H), 7.35 – 7.29 (m, 3H), 7.27 (s, 1H), 7.26 (s, 1H), 7.09 – 7.03 (m, 1H), 5.41 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.23, 138.69, 133.63, 132.74, 131.90, 128.68, 128.45, 128.27, 128.08, 127.84, 127.72, 126.40, 126.32, 126.06, 123.54, 122.02, 89.98, 84.55, 39.72.

HRMS calcd for $C_{23}H_{16}S$ [M+] 324.0973, found 324.0979.

HPLC analysis: 96% ee (Chiralcel OD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 13.1 min, minor R_t = 15.8 min).



(*S*)-3-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)furan ((*S*)-3.36c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

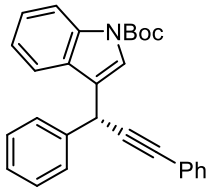
$[\alpha]_D^{25}$ = -17.9 (*c* .0014, DCM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 1.7 Hz, 1H), 7.85 (dd, *J* = 7.6, 4.7 Hz, 3H), 7.57 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.49 (qt, *J* = 4.0, 2.0 Hz, 4H), 7.46 (s, 1H), 7.38 (t, *J* = 1.8 Hz, 1H), 7.32 (p, *J* = 3.8, 3.2 Hz, 3H), 6.37 (d, *J* = 1.7 Hz, 1H), 5.25 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.61, 140.08, 138.27, 133.61, 132.78, 131.90, 128.67, 128.45, 128.28, 128.07, 127.84, 126.60, 126.39, 126.30, 126.29, 126.08, 123.47, 110.51, 89.55, 83.82, 35.19.

HRMS calcd for $C_{23}H_{16}O$ [M+] 308.1201, found 308.1202.

HPLC analysis: 96% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 24.8 min, minor R_t = 24.0 min).



***t*-butyl (*R*)-3-(1,3-diphenylprop-2-yn-1-yl)-1H-indole-1-carboxylate ((*R*)-3.37c)**

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

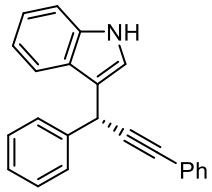
$[\alpha]_D^{25}$ = -26.6 (*c* .0047, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.57 – 7.50 (m, 3H), 7.46 (ddd, *J* = 5.4, 2.9, 1.7 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.32 – 7.27 (m, 5H), 7.19 – 7.13 (m, 1H), 5.38 (s, 1H), 1.67 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.97, 140.09, 136.08, 131.87, 128.82, 128.40, 128.20, 128.08, 127.32, 124.61, 124.10, 123.55, 122.68, 121.32, 120.10, 115.49, 89.36, 84.19, 83.92, 35.51, 28.38.

HRMS calcd for $C_{28}H_{25}NO_2$ [M+] 407.1885, found 407.1882.

HPLC analysis: Boc group removed substrate (**S3.22_c′**) was subjected to the HPLC separation due to the difficulty in separating (**S3.22c′**).



(*R*)-3-(1,3-diphenylprop-2-yn-1-yl)-1H-indole

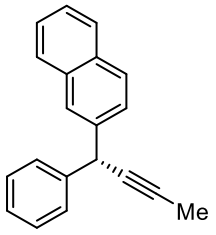
Dark brown oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 5.2 Hz, 1H), 7.54 (q, *J* = 6.9, 5.6 Hz, 3H), 7.47 (dt, *J* = 7.0, 3.5 Hz, 2H), 7.35 (q, *J* = 8.9, 8.2 Hz, 3H), 7.30 (q, *J* = 6.1, 4.7 Hz, 4H), 7.23 (d, *J* = 7.2 Hz, 1H), 5.38 (d, *J* = 4.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.68, 139.65, 136.14, 131.91, 129.59, 128.93, 128.67, 128.43, 128.31, 128.12, 127.51, 125.33, 123.67, 123.38, 120.36, 115.88, 88.89, 84.42, 35.56.

HRMS calcd for $C_{23}H_{17}N$ [M+] 307.1361, found 307.1369.

HPLC analysis: 96% ee (Chiralpak AD-H, 94:6 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 44.4 min, minor R_t = 48.3 min).



(*R*)-2-(1-phenylbut-2-yn-1-yl)naphthalene ((*R*)-3.44c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent

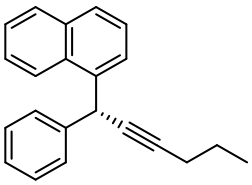
$[\alpha]_D^{25}$ = -9.9 (*c* .00142, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 1.7 Hz, 1H), 7.83 (s, 1H), 7.83 – 7.75 (m, 2H), 7.53 – 7.40 (m, 5H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 (s, 1H), 5.15 (q, *J* = 2.2 Hz, 1H), 1.98 (d, *J* = 2.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.27, 139.85, 133.59, 132.55, 128.70, 128.47, 128.13, 128.05, 127.77, 126.96, 126.54, 126.28, 126.25, 125.87, 81.04, 79.73, 43.56, 4.07.

HRMS calcd for $C_{20}H_{16}$ [M+] 256.1252, found 256.1255.

HPLC analysis: 96% ee (Chiralcel OD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 28.2 min, minor R_t = 29.8 min).



(*R*)-1-(1-phenylhex-2-yn-1-yl)naphthalene ((*R*)-3.46c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

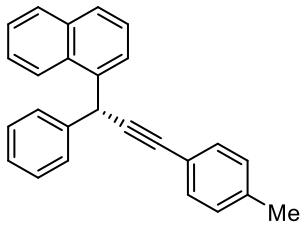
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 – 8.04 (m, 1H), 7.87 – 7.81 (m, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.40 – 7.34 (m, 2H), 7.26 (dd, *J* = 8.4, 6.8 Hz,

2H), 7.22 – 7.15 (m, 1H), 5.67 (d, *J* = 2.5 Hz, 1H), 2.23 (td, *J* = 7.0, 2.3 Hz, 2H), 1.62 – 1.48 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.96, 137.81, 134.26, 131.17, 128.90, 128.60, 128.10, 128.01, 126.78, 126.68, 126.10, 125.66, 125.64, 124.47, 85.65, 80.93, 40.42, 22.56, 21.21, 13.78.

HRMS calcd for $C_{22}H_{20}Na$ [M+Na] 307.1463, found 307.1460.

HPLC analysis: 96% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 24.7 min, minor R_t = 26.4 min).



(*R*)-1-(1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)naphthalene ((*R*)-3.47c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

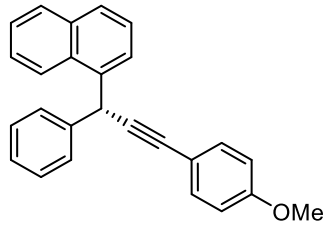
$[\alpha]_D^{25}$ = -53.3 (*c* .0003, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dt, *J* = 7.0, 3.6 Hz, 1H), 7.87 (dt, *J* = 6.9, 3.4 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 7.1 Hz, 1H), 7.52 – 7.41 (m, 5H), 7.38 – 7.28 (m, 5H), 7.22 (d, *J* = 76 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.92 (s, 1H), 2.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.35, 138.17, 137.18, 134.31, 131.72, 131.20, 129.12, 128.97, 128.72, 128.22, 128.19, 126.99, 126.90, 126.27, 125.76, 125.69, 124.39, 120.61, 89.67, 85.50, 40.96, 21.63.

HRMS calcd for $C_{26}H_{20}Na$ [M+Na] 355.1463, found 355.1459.

HPLC analysis: 96% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 19.2 min, minor R_t = 16.3 min).



(*R*)-1-(3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-yl)naphthalene ((*R*)-3.48c)

Yellow solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

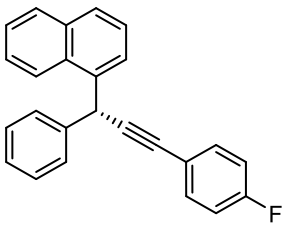
$[\alpha]_D^{25}$ = +43.2 (*c* .00074, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 6.3, 3.4 Hz, 1H), 7.88 (dd, *J* = 6.2, 3.4 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.47 (dt, *J* = 6.3, 3.2 Hz, 5H), 7.43 – 7.37 (m, 2H), 7.35 – 7.28 (m, 2H), 7.25 – 7.19 (m, 1H), 6.88 – 6.76 (m, 2H), 5.92 (s, 1H), 3.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.49, 141.42, 137.26, 134.31, 133.22, 131.20, 128.96, 128.71, 128.18, 126.97, 126.88, 126.25, 125.75, 125.68, 124.40, 115.84, 113.97, 88.91, 85.23, 55.44, 40.96.

HRMS calcd for $C_{26}H_{20}O$ [M+] 348.1514, found 348.1519.

HPLC analysis: 96% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 32.1 min, minor R_t = 25.5 min).



(*R*)-1-(3-(4-fluorophenyl)-1-phenylprop-2-yn-1-yl)naphthalene ((*R*)-3.49c)

Yellow oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

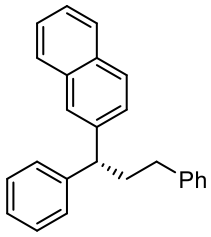
$[\alpha]_D^{25}$ = -24 (*c* .0005, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.07 (m, 1H), 7.91 – 7.85 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.0 Hz, 1H), 7.46 (ddt, *J* = 12.9, 8.0, 4.1 Hz, 8H), 7.35 – 7.28 (m, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.91 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.49 (d, *J* = 248.9 Hz), 141.09, 136.92, 133.69 (d, *J* = 8.2 Hz), 131.16, 130.61, 129.02, 128.79, 128.33, 128.16, 127.10, 126.86, 126.33, 125.82, 125.68, 124.30, 119.74 (d, *J* = 3.6 Hz), 115.61 (d, *J* = 21.8 Hz), 90.10, 84.35, 40.89.

HRMS calcd for $C_{25}H_{18}F$ [M+H] 337.1393, found 337.1404.

HPLC analysis: 96% ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 15.4 min, minor R_t = 13.9 min).



(*R*)-2-(1,3-diphenylpropyl)naphthalene ((*R*)-3.17e)

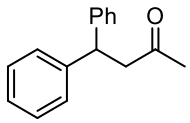
Colorless oil isolated from flash chromatography using: 49:1 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 11.0 Hz, 2H), 7.76 – 7.70 (m, 2H), 7.44 (td, *J* = 7.5, 1.5 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.28 (m, 5H), 7.26 (s, 1H), 7.23 – 7.12 (m, 4H), 4.09 (t, *J* = 7.6 Hz, 1H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.57 – 2.41 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 144.86, 142.40, 142.27, 133.71, 132.34, 128.69, 128.65, 128.55, 128.33, 128.19, 127.89, 127.75, 126.91, 126.43, 126.15, 126.12, 126.02, 125.60, 50.85, 37.28, 34.29.

HRMS calcd for $C_{25}H_{21}$ [M-H] 321.1643, found 321.1648.

HPLC analysis: 78% ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.2 mL/min, 254 nm, major R_t = 32.7 min, minor R_t = 37.5 min).



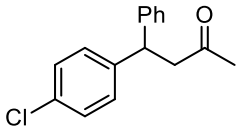
4,4-diphenylbutan-2-one (3.55c)

Yellow oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 4H), 7.22 – 7.17 (m, 4H), 7.15 (dd, *J* = 7.0, 1.6 Hz, 2H), 4.56 (t, *J* = 7.4 Hz, 1H), 3.15 (d, *J* = 7.5 Hz, 2H), 2.04 (d, *J* = 2.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.03, 143.99, 128.74, 127.85, 126.60, 49.81, 46.17, 30.82.

HRMS calcd for $C_{16}H_{16}ONa$ [M+Na] 247.1099, found 247.1132.



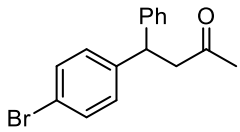
4-(4-chlorophenyl)-4-phenylbutan-2-one (3.56c)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 1.3 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.17 (td, *J* = 5.8, 5.3, 2.8 Hz, 3H), 7.15 – 7.11 (m, 2H), 4.55 (t, *J* = 7.5 Hz, 1H), 3.14 (d, *J* = 7.5 Hz, 2H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.63, 143.53, 142.57, 132.38, 129.26, 128.88, 127.78, 126.84, 49.65, 45.44, 30.86.

HRMS calcd for $C_{16}H_{15}ClONa$ [M+Na] 281.0709, found 281.0714.



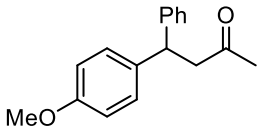
4-(4-bromophenyl)-4-phenylbutan-2-one (3.57c)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 2H), 7.30 – 7.24 (m, 2H), 7.19 (td, *J* = 6.6, 1.6 Hz, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 4.55 (t, *J* = 7.5 Hz, 1H), 3.15 (d, *J* = 7.5 Hz, 2H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.61, 143.44, 143.11, 131.83, 129.66, 128.89, 127.79, 126.86, 120.48, 49.59, 45.50, 30.86.

HRMS calcd for $C_{16}H_{15}BrONa$ [M+Na] 325.0204, found 325.0194.



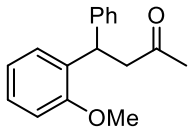
4-(4-methoxyphenyl)-4-phenylbutan-2-one (3.58c)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.52 (m, 2H), 7.52 – 7.48 (m, 2H), 7.48 – 7.38 (m, 3H), 7.13 – 7.06 (m, 2H), 4.82 (t, *J* = 7.6 Hz, 1H), 4.03 (s, 3H), 3.43 (d, *J* = 7.6 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.19, 158.21, 144.35, 136.09, 128.78, 128.70, 127.72, 126.50, 114.07, 55.32, 50.00, 45.40, 30.80.

HRMS calcd for $C_{17}H_{18}O_2Na$ [M+Na] 277.1205, found 277.1220.



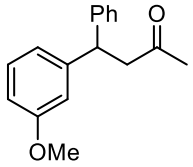
4-(2-methoxyphenyl)-4-phenylbutan-2-one (3.59c)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 4.9 Hz, 4H), 7.25 – 7.17 (m, 2H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.97 – 6.90 (m, 1H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.03 (t, *J* = 7.7 Hz, 1H), 3.83 (s, 3H), 3.19 (dd, *J* = 7.8, 2.5 Hz, 2H), 2.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.53, 156.86, 143.55, 132.31, 128.44, 128.10, 127.98, 127.70, 126.31, 120.68, 110.93, 55.54, 49.02, 39.61, 30.35.

HRMS calcd for $C_{17}H_{17}O_2$ [M+] 253.1229, found 253.1212.



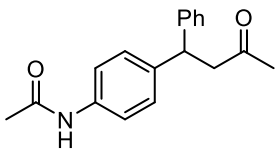
4-(3-methoxyphenyl)-4-phenylbutan-2-one (3.60c)

Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 7.24 – 7.20 (m, 2H), 7.20 – 7.13 (m, 2H), 6.82 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.77 (s, 1H), 6.72 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.55 (t, *J* = 7.5 Hz, 1H), 3.76 (s, 3H), 3.16 (d, *J* = 7.6 Hz, 2H), 2.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.02, 159.85, 145.64, 143.86, 129.73, 128.77, 127.84, 126.66, 120.23, 114.11, 111.52, 55.31, 49.79, 46.19, 30.86.

HRMS calcd for $C_{17}H_{18}O_2$ [M+] 254.1307, found 254.1314.



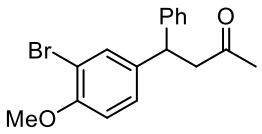
N-(4-(3-oxo-1-phenylbutyl)phenyl)acetamide (3.62c)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 2H), 7.14 – 7.07 (m, 2H), 7.02 (ddd, *J* = 15.6, 6.8, 4.0 Hz, 5H), 4.39 (t, *J* = 7.6 Hz, 1H), 3.00 (d, *J* = 7.6 Hz, 2H), 1.97 (s, 3H), 1.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.21, 168.53, 143.92, 139.91, 136.41, 128.77, 128.37, 127.79, 126.65, 120.30, 49.81, 45.61, 30.86, 24.66.

HRMS calcd for $C_{18}H_{19}NO_2Na$ [M+Na] 304.1313, found 304.1301.



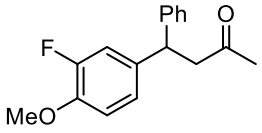
4-(3-bromo-4-methoxyphenyl)-4-phenylbutan-2-one (3.65c)

Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 2.2 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.20 – 7.14 (m, 3H), 7.11 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 4.50 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.12 (d, *J* = 7.5 Hz, 2H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.70, 154.56, 143.70, 137.77, 132.54, 128.88, 127.96, 127.74, 126.80, 112.09, 111.88, 56.40, 49.78, 44.98, 30.88.

HRMS calcd for $C_{17}H_{17}BrO_2Na$ [M+Na] 355.0310, found 355.0346.



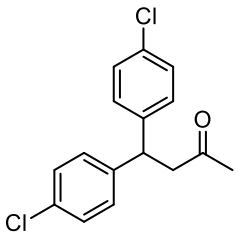
4-(3-fluoro-4-methoxyphenyl)-4-phenylbutan-2-one (3.66c)

Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 2H), 7.15 (dt, *J* = 5.9, 1.6 Hz, 3H), 6.94 – 6.86 (m, 2H), 6.82 (t, *J* = 8.7 Hz, 1H), 4.48 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.10 (d, *J* = 7.5 Hz, 2H), 2.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.76, 152.44 (d, J = 245.9 Hz), 146.23 (d, *J* = 10.8 Hz), 143.74, 137.18 (d, *J* = 5.6 Hz), 128.85, 127.71, 126.79, 123.44, 115.56 (d, *J* = 18.7 Hz), 113.54, 56.42, 49.76, 45.17, 30.86.

HRMS calcd for $C_{17}H_{17}FO_2Na$ [M+Na] 295.1110, found 295.1101.



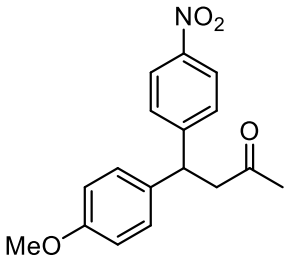
4,4-bis(4-chlorophenyl)butan-2-one (3.67c)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.22 (m, 4H), 7.20 – 7.09 (m, 4H), 4.57 (t, *J* = 7.5 Hz, 1H), 3.16 (d, *J* = 7.5 Hz, 2H), 2.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.18, 142.07, 132.61, 129.17, 128.99, 49.47, 44.69, 30.84.

HRMS calcd for $C_{16}H_{14}Cl_2O$ [M+] 292.0422, found 292.0406.



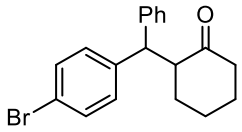
4-(4-methoxyphenyl)-4-(4-nitrophenyl)butan-2-one (3.68c)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.65 (t, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 3.26 – 3.11 (m, 2H), 2.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.04, 158.69, 152.14, 146.63, 134.46, 128.83, 128.68, 124.02, 114.46, 55.43, 49.40, 44.97, 30.82.

HRMS calcd for $C_{17}H_{17}NO_4$ [M+] 299.1158, found 299.1126.



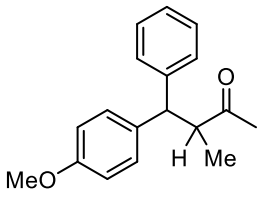
2-((4-bromophenyl)(phenyl)methyl)cyclohexan-1-one (3.69c)

Colorless liquid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, CDCl3): δ 7.37 (d, *J* = 8.5 Hz, 2H), 7.25 – 7.21 (m, 4H), 7.18 – 7.11 (m, 1H), 7.11 – 7.03 (m, 2H), 4.30 (d, *J* = 10.5 Hz, 1H), 3.31 (td, *J* = 10.7, 4.6 Hz, 1H), 2.52 – 2.31 (m, 2H), 2.05 (dqd, *J* = 12.2, 4.2, 2.2 Hz, 1H), 1.84 (dddt, *J* = 10.1, 8.0, 5.1, 2.0 Hz, 2H), 1.79 – 1.60 (m, 2H), 1.36 (dd, *J* = 10.4, 2.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 212.07, 143.48, 142.31, 131.84, 130.35, 128.72, 127.65, 126.53, 120.35, 54.77, 50.41, 42.80, 33.61, 29.27, 24.93.

HRMS calcd for $C_{19}H_{19}BrONa$ [M+Na] 365.0517, found 365.0514.



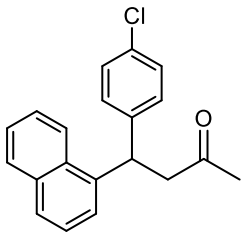
4-(4-methoxyphenyl)-3-methyl-4-phenylbutan-2-one (3.70c)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.21 (m, 4H), 7.17 (dd, *J* = 7.6, 5.1 Hz, 3H), 6.88 – 6.65 (m, 2H), 4.00 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.73 (d, *J* = 13.0 Hz, 3H), 3.43 (dq, *J* = 11.1, 6.8 Hz, 1H), 1.97 (d, *J* = 4.5 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 212.54, 158.25, 142.96, 135.56, 128.84, 128.80, 128.20, 126.64, 114.20, 55.33, 54.15, 51.82, 29.47, 16.70.

HRMS calcd for $C_{18}H_{20}O_2Na$ [M+Na] 291.1361, found 291.1357.



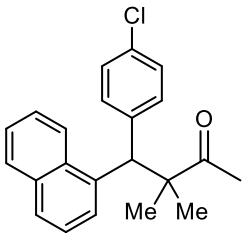
4-(4-chlorophenyl)-4-(naphthalen-1-yl)butan-2-one (3.71c)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.70 (m, 3H), 7.66 – 7.60 (m, 1H), 7.44 (ddd, *J* = 8.4, 5.9, 1.8 Hz, 2H), 7.29 – 7.20 (m, 3H), 7.18 (d, *J* = 8.5 Hz, 2H), 4.73 (t, *J* = 7.5 Hz, 1H), 3.34 – 3.13 (m, 2H), 2.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.58, 142.42, 140.93, 133.58, 132.46, 132.41, 129.41, 128.91, 128.66, 127.92, 127.77, 126.53, 126.41, 125.95, 125.84, 49.52, 45.48, 30.92.

HRMS calcd for $C_{20}H_{17}ClONa$ [M+Na] 331.0866, found 331.0861.



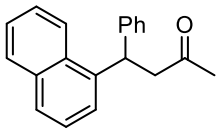
4-(4-chlorophenyl)-3,3-dimethyl-4-(naphthalen-1-yl)butan-2-one (3.72c)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (ddd, *J* = 7.5, 5.7, 1.8 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.41 (ddd, *J* = 7.2, 5.5, 1.7 Hz, 2H), 7.24 – 7.13 (m, 5H), 4.55 (s, 1H), 2.02 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 213.32, 140.09, 138.73, 133.26, 132.65, 132.27, 131.48, 128.49, 128.46, 128.18, 128.08, 128.05, 127.64, 126.37, 126.12, 57.67, 51.80, 26.12, 24.37, 24.02.

HRMS calcd for $C_{22}H_{21}ClONa$ [M+Na] 359.1179, found 359.1185.



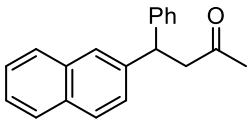
4-(naphthalen-1-yl)-4-phenylbutan-2-one (3.73c)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 – 8.09 (m, 1H), 7.83 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.35 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.30 – 7.20 (m, 4H), 7.21 – 7.11 (m, 1H), 5.43 (t, *J* = 7.4 Hz, 1H), 3.30 (dd, *J* = 7.4, 5.5 Hz, 2H), 2.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.03, 143.86, 139.44, 134.30, 131.65, 129.02, 128.77, 128.07, 127.59, 126.62, 126.39, 125.76, 125.42, 124.44, 123.91, 50.35, 41.70, 30.82.

HRMS calcd for $C_{20}H_{18}O$ 274.1358 [M+], found 274.1356.



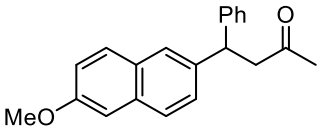
4-(naphthalen-2-yl)-4-phenylbutan-2-one (3.74c)

White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.70 (m, 3H), 7.67 (d, *J* = 1.8 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.34 – 7.29 (m, 1H), 7.29 – 7.23 (m, 4H), 7.18 (dqd, *J* = 8.3, 5.6, 2.8 Hz, 1H), 4.75 (t, *J* = 7.5 Hz, 1H), 3.37 – 3.17 (m, 2H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.02, 143.85, 141.43, 133.60, 132.37, 128.79, 128.50, 128.01, 127.93, 127.74, 126.72, 126.70, 126.27, 125.86, 125.79, 49.69, 46.24, 30.91.

HRMS calcd for $C_{20}H_{18}ONa$ [M+] 297.1255, found 297.1263.



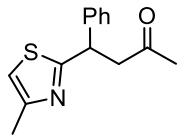
4-(6-methoxynaphthalen-2-yl)-4-phenylbutan-2-one (3.75c)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.30 – 7.23 (m, 5H), 7.18 (td, *J* = 6.4, 2.6 Hz, 1H), 7.12 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 4.72 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 3.26 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.17, 157.68, 144.08, 139.15, 133.44, 129.42, 129.06, 128.77, 127.99, 127.37, 127.21, 126.64, 125.74, 119.04, 105.75, 55.49, 49.82, 46.12, 30.92.

HRMS calcd for $C_{21}H_{21}O_2$ [M+H] 305.1542, found 305.1582.



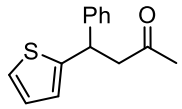
4-(4-methylthiazol-2-yl)-4-phenylbutan-2-one (3.77c)

Yellow solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 3H), 7.19 (s, 2H), 6.64 (d, *J* = 1.2 Hz, 1H), 4.78 (t, *J* = 7.2 Hz, 1H), 3.57 (dd, *J* = 17.3, 7.7 Hz, 1H), 3.01 (dd, *J* = 17.3, 6.8 Hz, 1H), 2.33 (d, *J* = 1.0 Hz, 3H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.42, 172.37, 152.20, 142.13, 128.96, 128.11, 127.46, 113.66, 49.37, 44.73, 30.73, 17.34.

HRMS calcd for $C_{14}H_{16}NOS$ [M+H] 246.0953, found 246.0940.



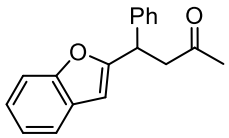
4-phenyl-4-(thiophen-2-yl)butan-2-one (3.78c)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.21 (m, 4H), 7.21 – 7.13 (m, 1H), 7.09 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.86 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.76 (dt, *J* = 3.6, 1.1 Hz, 1H), 4.78 (t, *J* = 7.4 Hz, 1H), 3.22 (dd, *J* = 16.7, 7.4 Hz, 1H), 3.12 (dd, *J* = 16.7, 7.4 Hz, 1H), 2.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.39, 148.19, 143.66, 128.84, 127.72, 127.07, 126.85, 124.32, 124.03, 51.14, 41.76, 30.83.

HRMS calcd for $C_{14}H_{14}OSNa$ [M+Na] 253.0663, found 253.0656.



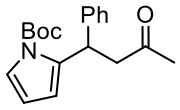
4-(benzofuran-2-yl)-4-phenylbutan-2-one (3.79c)

Yellow liquid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.27 – 7.21 (m, 2H), 7.17 (dt, *J* = 14.8, 7.5 Hz, 2H), 6.38 (s, 1H), 4.74 (t, *J* = 7.3 Hz, 1H), 3.36 (dd, *J* = 17.0, 7.3 Hz, 1H), 3.11 (dd, *J* = 17.0, 7.4 Hz, 1H), 2.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.05, 159.78, 154.94, 141.09, 128.90, 128.65, 128.08, 127.33, 123.79, 122.80, 120.77, 111.16, 103.07, 48.21, 40.70, 30.67.

HRMS calcd for $C_{18}H_{16}O_2Na$ [M+Na] 287.1048, found 287.1044.



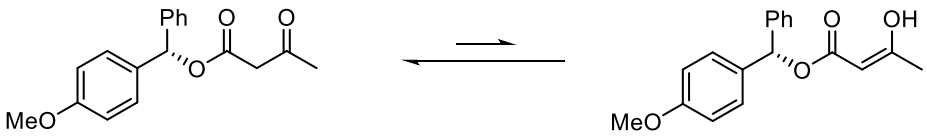
tert-butyl 2-(3-oxo-1-phenylbutyl)-1H-pyrrole-1-carboxylate (3.81c)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 7.21 – 7.16 (m, 1H), 7.14 (dt, *J* = 7.8, 1.9 Hz, 3H), 6.10 (t, *J* = 3.4 Hz, 1H), 6.04 (t, *J* = 2.5 Hz, 1H), 5.31 (t, *J* = 7.6 Hz, 1H), 3.13 (dd, *J* = 16.5, 7.7 Hz, 1H), 2.95 (dd, *J* = 16.4, 7.7 Hz, 1H), 2.10 (s, 3H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.93, 149.22, 143.34, 136.92, 128.44, 128.01, 126.51, 122.13, 111.77, 109.84, 83.80, 50.75, 39.33, 30.34, 28.02.

HRMS calcd for $C_{19}H_{23}NO_3Na$ [M+Na] 336.1576, found 336.1569.



(*S*)-3.58b

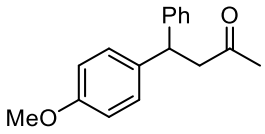
Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.97 (s, 0.09H), 7.40 – 7.36 (m, 1H), 7.34 (dd, *J* = 6.8, 1.5 Hz, 4H), 7.32 – 7.26 (m, 3H), 7.25 (d, *J* = 1.9 Hz, 1H), 6.92 – 6.84 (m, 4H), 5.82 (d, *J* = 3.4 Hz, 0.28H), 3.79 (s, 4H), 3.54 (s, 2H), 2.22 (s, 3H), 2.17 (d, *J* = 4.8 Hz, 0.3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.23, 200.55, 176.28, 171.86, 166.39, 159.59, 159.46, 159.21, 144.18, 140.51, 139.87, 136.34, 131.88, 128.97, 128.80, 128.69, 128.61, 128.14, 128.08, 127.60, 127.08, 126.56, 114.08, 90.03, 77.87, 76.30, 75.98, 55.45, 50.53, 31.12, 30.35, 21.45.

HRMS calcd for $C_{18}H_{18}O_4Na$ [M+Na] 321.1103, found 321.1114.

HPLC analysis: 91%ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R*t* = 32.5 min, major R*t* = 23.7 min).



4-(4-methoxyphenyl)-4-phenylbutan-2-one (3.58c)

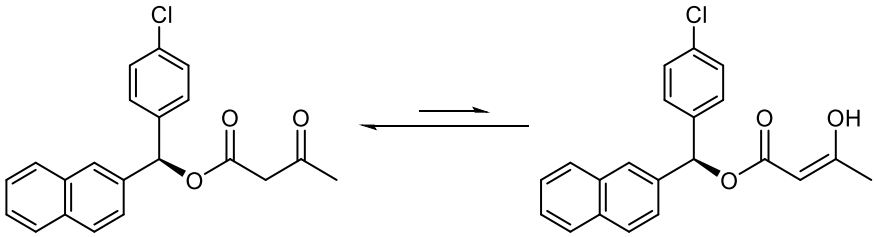
White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.25 (s, 1H), 7.23 – 7.16 (m, 3H), 7.16 – 7.10 (m, 2H), 6.85 – 6.78 (m, 2H), 4.53 (s, 1H), 3.76 (s, 3H), 3.15 (d, *J* = 7.6 Hz, 2H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.19, 158.21, 144.35, 136.09, 128.78, 128.70, 127.72, 126.50, 114.07, 55.32, 50.00, 45.40, 30.80.

HRMS calcd for $C_{17}H_{18}O_2Na$ [M+Na] 277.1205, found 277.1198.

HPLC analysis: 1%ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, R*t* = 23.7 min, 27.3 min).



(*R*)-3.71b

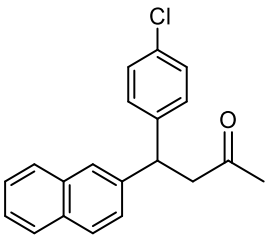
Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 0.12H), 7.82 (dtd, *J* = 7.9, 5.8, 2.5 Hz, 6H), 7.55 – 7.45 (m, 3H), 7.38 (ddd, *J* = 10.6, 8.5, 1.9 Hz, 3H), 7.33 (s, 5H), 7.05 (d, *J* = 2.0 Hz, 1H), 5.99 (d, *J* = 3.4 Hz, 0.47H), 3.59 (d, *J* = 2.3 Hz, 2H), 2.31 (dd, *J* = 3.5, 1.6 Hz, 0.5H), 2.25 (d, *J* = 2.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.15, 176.62, 171.54, 166.12, 142.06, 140.73, 138.60, 137.96, 136.96, 136.31, 134.12, 132.97, 128.82, 128.77, 128.68, 128.67, 128.58, 128.18, 128.06, 127.72, 126.56, 126.54, 126.46, 126.43, 126.37, 126.34, 126.19, 126.03, 125.17, 124.73, 124.70, 124.57, 89.68, 77.41, 75.82, 50.28, 30.28, 21.35.

HPLC analysis: 87%ee (Chiralcel OD, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R*t* = 75.4 min, major R*t* = 82.8 min).

HRMS calcd for $C_{21}H_{17}ClO_3Na$ [M+Na] 375.0764, found 375.0762.



4-(4-chlorophenyl)-4-(naphthalen-1-yl)butan-2-one (3.71c)

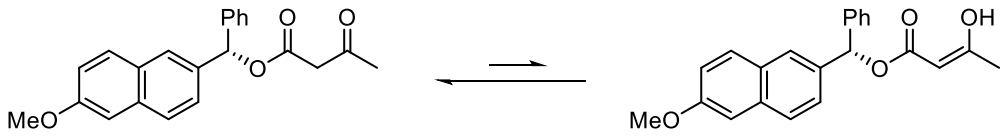
White solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 16.4, 8.3 Hz, 3H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.44 (td, *J* = 7.9, 1.5 Hz, 2H), 7.29 – 7.20 (m, 3H), 7.20 – 7.14 (m, 2H), 4.72 (s, 1H), 3.32 – 3.15 (m, 2H), 2.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 206.59, 142.42, 140.94, 133.58, 132.47, 132.42, 129.41, 128.91, 128.67, 127.92, 127.78, 126.53, 126.42, 125.96, 125.84, 49.52, 45.49, 30.93.

HPLC analysis: 1%ee (Chiralcel OD, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, R*t* = 53.1 min, 66.09 min).

HRMS calcd for $C_{20}H_{17}ClOLi$ [M+Li] 315.1128, found 315.1127.



(S)-3.75b

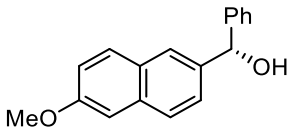
(The racemic substrate could not separate by HPLC using OD, AD, OD-H and AS-H chiral columns)

Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$):δ 11.97 (s, 0.09H), 7.81 (s, 0.3H), 7.74 (d, *J* = 5.0 Hz, 2H), 7.71 (d, *J* = 2.8 Hz, 1H), 7.69 (d, *J* = 3.7 Hz, 1H), 7.42 (s, 1H), 7.40 – 7.34 (m, 5H), 7.34 – 7.28 (m, 2H), 7.16 (s, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.07 (s, 1H), 5.99 (d, *J* = 3.4 Hz, 0.32H), 3.91 (s, 4H), 3.58 (s, 2H), 2.27 (s, 0.33H), 2.23 (s, 3H).

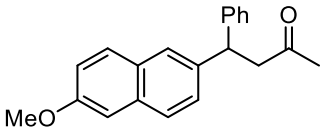
^{13}C NMR (126 MHz, $CDCl_3$): δ 200.52, 176.40, 166.42, 158.25, 157.96, 143.96, 139.71, 139.11, 134.71, 134.42, 134.21, 129.84, 129.80, 129.72, 128.83, 128.75, 128.69, 128.64, 128.28, 128.09, 127.77, 127.49, 127.40, 127.35, 127.25, 126.83, 126.46, 126.16, 125.69, 125.52, 125.20, 90.04, 78.32, 76.74, 76.53, 55.50, 50.56, 31.14, 30.38, 21.49.

HRMS calcd for $C_{22}H_{20}O_4Na$ [M+Na] 371.1259, found 371.1262.



(*S*)-(6-methoxynaphthalen-2-yl)(phenyl)methanol ((*S*)-3.75a)

HPLC analysis: 95% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R*t* = 88.3 min, major R*t* = 51.8 min).



4-(6-methoxynaphthalen-2-yl)-4-phenylbutan-2-one (3.75c)

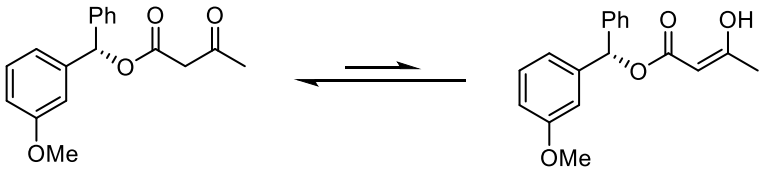
White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 15.2, 8.7 Hz, 2H), 7.62 – 7.58 (m, 1H), 7.30 (d, *J* = 1.9 Hz, 1H), 7.27 (d, *J* = 3.9 Hz, 2H), 7.26 (s, 2H), 7.21 – 7.15 (m, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 4.72 (t, *J* = 7.5 Hz, 1H), 3.90 (s, 3H), 3.26 (dd, *J* = 7.5, 4.8 Hz, 2H), 2.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.17, 157.68, 144.08, 139.15, 133.44, 129.42, 129.06, 128.77, 127.99, 127.37, 127.21, 126.64, 125.74, 119.04, 105.75, 55.49, 49.82, 46.12, 30.92.

HRMS calcd for $C_{21}H_{21}O_2$ [M+H] 305.1542, found 305.1538.

HPLC analysis: 1% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, R*t* = 36.8 min, 39.9 min).



(*S*)-3.60b

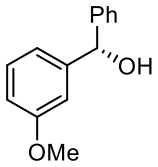
(The racemic substrate could not separate by HPLC using OD, AD, OD-H and AS-H chiral columns)

Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.94 (s, 0.09H), 7.42 – 7.36 (m, 1H), 7.36 – 7.31 (m, 5H), 7.31 – 7.27 (m, 1H), 7.26 (s, 2H), 7.24 (s, 1H), 6.96 (s, 1H), 6.93 – 6.86 (m, 3H), 6.82 (d, *J* = 1.8 Hz, 2H), 5.82 (d, *J* = 3.4 Hz, 0.48H), 3.85 – 3.74 (m, 5H), 3.55 (d, *J* = 1.8 Hz, 2H), 2.23 (d, *J* = 1.7 Hz, 3H), 2.21 (d, *J* = 3.6 Hz, 0.55H).

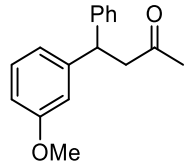
^{13}C NMR (126 MHz, $CDCl_3$): δ 200.43, 166.31, 159.87, 145.62, 143.83, 141.21, 139.56, 129.80, 129.71, 128.75, 128.69, 128.37, 127.81, 127.37, 126.70, 119.56, 119.05, 113.56, 113.14, 112.99, 112.24, 89.97, 78.69, 78.01, 76.35, 55.43, 50.47, 30.39, 29.36, 21.48, 10.08.

HRMS calcd for $C_{18}H_{18}O_4Na$ [M+Na] 321.1103, found 321.1101.



(*S*)-(3-methoxyphenyl)(phenyl)methanol ((*S*)-3.60a)

HPLC analysis: 95% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R*t* = 70.9 min, major R*t* = 46.1 min).



4-(3-methoxyphenyl)-4-phenylbutan-2-one (3.60c)

(HPLC analysis carried out for the crude of the reaction without further purification)

HRMS calcd for $C_{17}H_{18}O_2Na$ [M+Na] 277.1205, found 277.1216.

HPLC analysis: 1% ee (Chiralcel OD-H, 95:5 Hexanes/isopropanol, 0.5 mL/min, 254 nm, R*t* = 45.5 min, 55.2 min).

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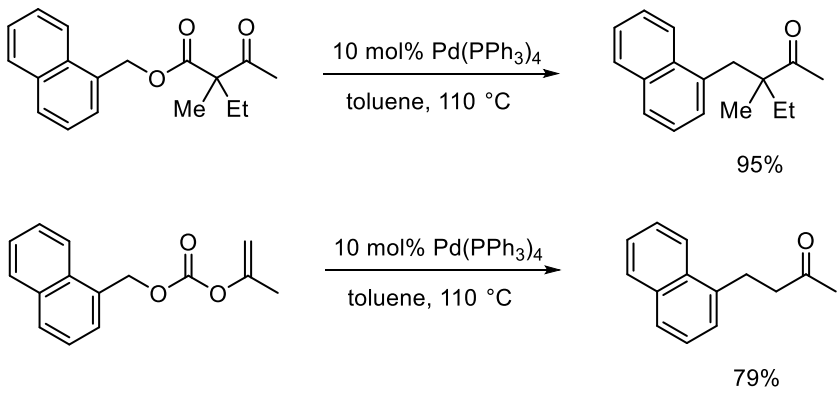
Chapter 4:

Palladium-Catalyzed Decarboxylative Dearomatizations and Arylations of Ketone Enolates

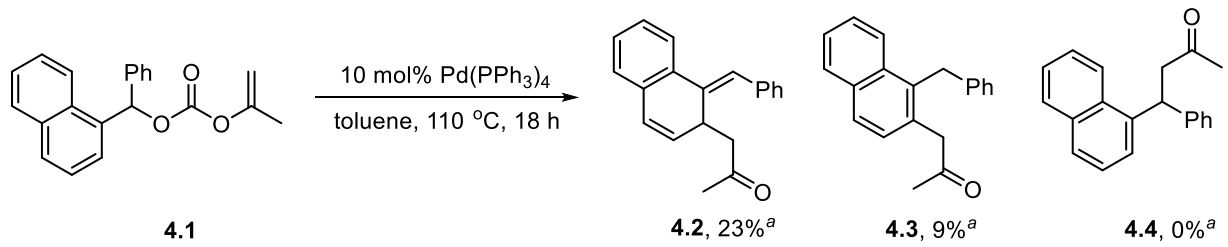
4.1 Palladium-catalyzed dearomatization

4.1.1 Introduction

Palladium-catalyzed decarboxylative cross-coupling reactions have enabled transformations that are either difficult or previously unknown via conventional methods. In this regard, palladium-catalyzed decarboxylative benzylation reactions offer a powerful strategy for benzylic alkylation of less-stabilized nucleophiles (pK_a >20).[1] For example, benzyl β-keto esters and benzyl enol carbonates are known to undergo palladium-catalyzed decarboxylative benzylation to provide benzylated ketones (Scheme 4.1).[1a, 2] Nevertheless, our initial attempts to perform a similar coupling with 1,1-diarylmethyl enol carbonate (**4.1**) provided the dearomatized (**4.2**) and arylated ketones (**4.3**) in very low yield and did not generate benzylated product (**4.4**) (Scheme 4.2). While methods for catalytic dearomatization and arylation of ketones are of high synthetic value, to the best of our knowledge, there are no literature reports of catalytic decarboxylative dearomatization or decarboxylative arylation of ketones that proceed via the intermediacy of palladium-π-benzyl intermediates. Thus, it became our goal to develop useful synthetic methods for decarboxylative dearomatizations and decarboxylative arylations.



Scheme 4.1



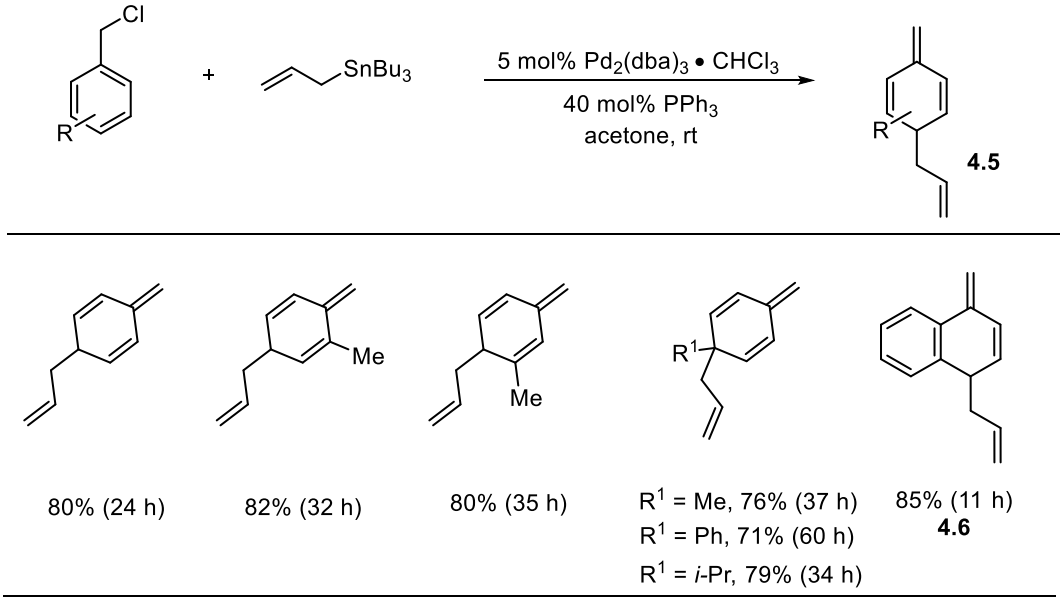
[a] %conversion calculated from ^{1}H NMR.

Scheme 4.2

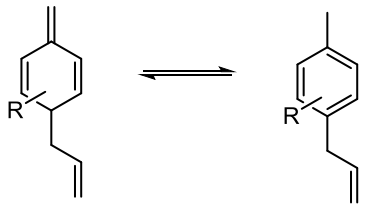
Dearomatization of arenes has attracted much attention due to its potential to generate alicyclic carbocycles, which are ubiquitous intermediates in natural product synthesis.[3] Birch reduction and photocycloaddition of arenes to alkenes are two of the most common ways to achieve similar dearomatizations.[4] The transition metal-mediated dearomatization reactions are generally limited to two basic methods:[5] (i) electrophilic reactions that proceed via the coordination and activation of more electron rich π-basic metals to arenes [M(η^2-arene)] (M = Os, Re, Mo, W) and (ii) nucleophilic dearomatization reactions via arene coordination and activation by more electron deficient metals [M(η^6-arene)] (M = Cr, Mn, Ru).

In addition to the aforementioned metal-mediated reactions, Bao and Yamamoto reported a palladium-catalyzed allylative dearomatization that involves the intermediacy of η^3-palladium-π-benzyl intermediates which react with allyltributyltin reagent (Scheme 4.3).[6] In this report the coupling of benzyl chloride and allyltributylstannane in the presence of 5 mol% Pd_2dba_3•$CHCl_3$ and 40 mol% PPh_3 in acetone resulted in the formation of **4.5**, without generating the Stille coupling products. Having a methyl substituent at the ortho, meta or para position did not heavily affect the formation of the dearomatized product but, depending on the steric hindrance, longer reaction times were required. Remarkably, 1-naphthylmethyl chloride reacted more rapidly than benzene derivatives and yielded **4.6** in 85% yield in 11 hours. The dearomatized products were

stable in $CDCl_3$ for days at ambient temperature, and for weeks in a refrigerator. Eventually, the dearomatized products **4.7** underwent slow isomerization to the re-aromatized products **4.8**. This type of isomerization was also observed during purification step using silica as the stationary phase for column chromatography, therefore these compounds were purified on a basic alumina column.

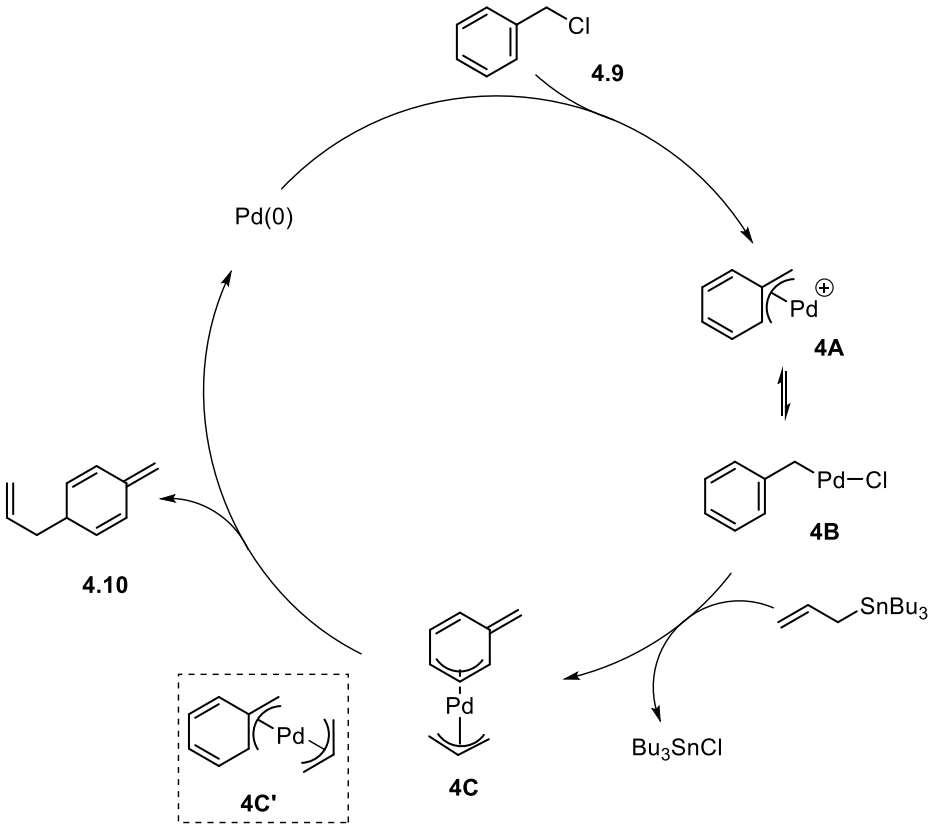


Scheme 4.3

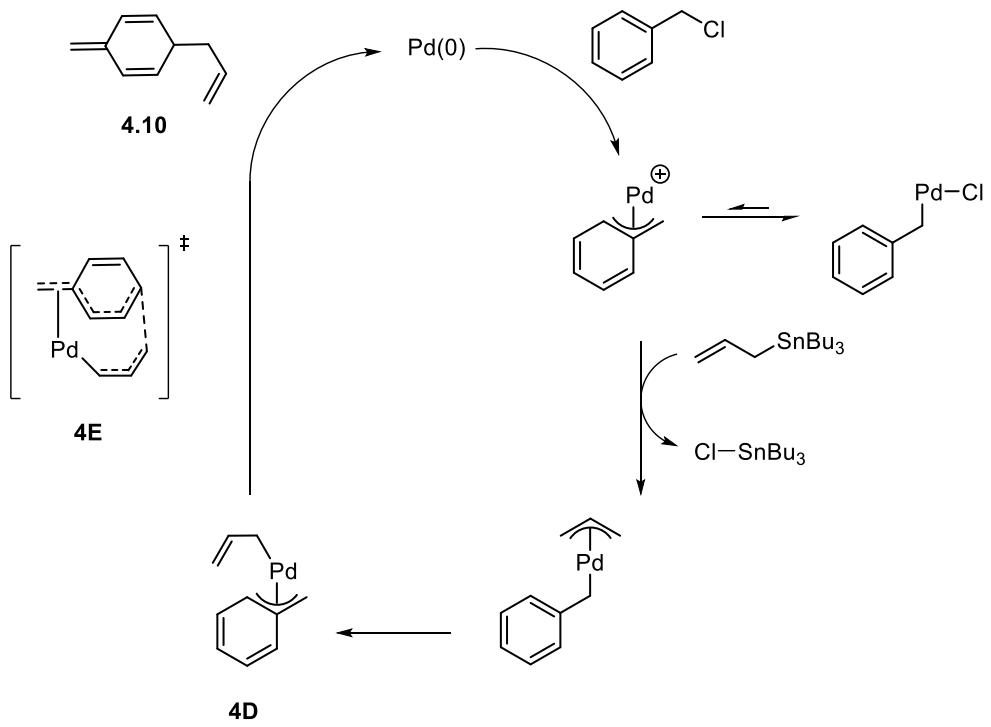


In the catalytic cycle proposed by Yamamoto, oxidative addition of benzyl chloride **4.9** to Pd(0), generates the Pd(II) intermediate (Scheme 4.4). This Pd(II) intermediate can isomerize between η^3-(**4A**) and η^1-Pd-benzyl (**4B**) intermediates.[6] Transmetallation of **4B** with allyltributylstannane generates a bis-π-allyl-Pd intermediate (**4C**). Reductive elimination of **4C**

yields the dearomatized product **4.10**. The generation of regioisomeric bis-π-allyl-Pd intermediate **4C′** is also possible, but product **4.10** is proposed to arise via the reductive coupling of intermediate **4C**. However, the DFT calculations performed by Lin have shown that the generation of intermediate **4C** is energetically unfavorable, and a new mechanism was proposed (Scheme 4.5).[7] The main difference is that the reductive elimination occurs directly from **4D** via **4E**-type intermediate in which the direct coupling of the C3-carbon of η^1-palladium-allyl with the *para*-carbon of the η^3-palladium-benzyl generates the product **4.10**.



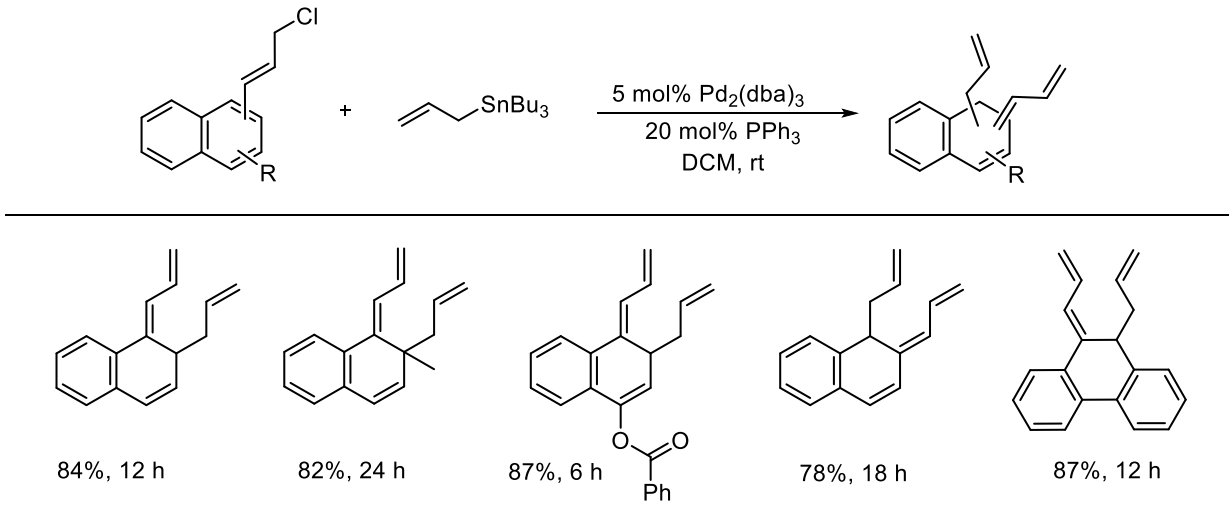
Scheme 4.4



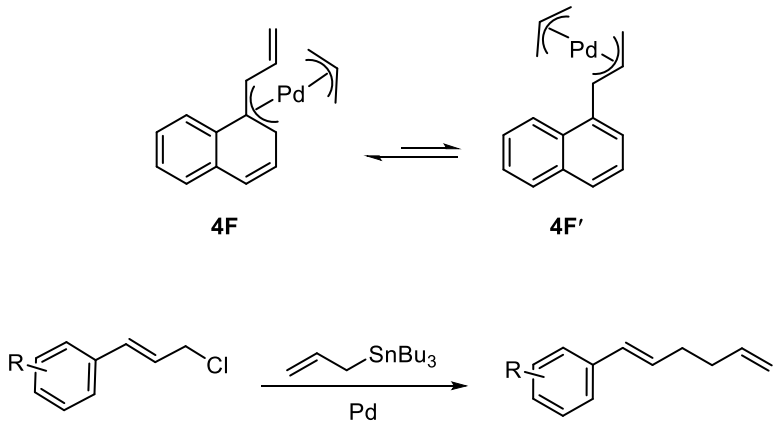
Scheme 4.5

The palladium-catalyzed allylative dearomatization was also reported with naphthalene and phenanthrene allyl chlorides in the presence of 5 mol% $Pd_2(dba)_3$ and 20 mol% PPh_3 in DCM at room temperature (Scheme 4.6).[8] Interestingly, the previously observed para selectivity for allylation was no longer seen,[6] rather the ortho allylated products were formed via intermediates **4F** and **4F′**.

As expected, the dearomatized products obtained from naphthalene and phenanthrene allyl chlorides were far more stable than the products obtained from benzyl chlorides, and these were purified via a silica column without any isomerization. Furthermore, varying the electronics of the aryl rings did not significantly affect the reaction yield. However, under optimized conditions, cinnamyl chloride derivatives did not provide any dearomatized products, but indeed underwent Stille coupling (Scheme 4.7).

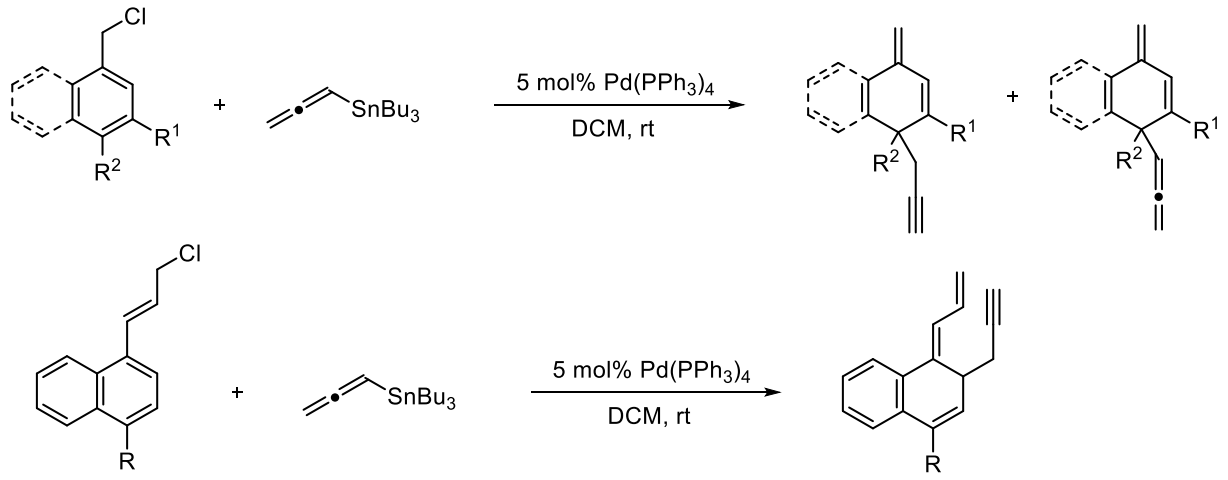


Scheme 4.6



Scheme 4.7

In addition to the above reports, Bao further demonstrated the allylative dearomatization of benzyl chlorides, naphthalenemethyl chlorides and naphthalene allyl chlorides, resulting in propargylated and/or allenylated dearomatized products in the presence of allenyltributylstannane and catalytic $Pd(PPh_3)_4$ (Scheme 4.8).[9]



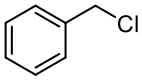
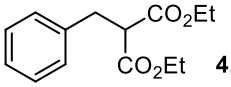
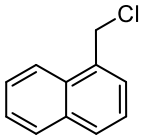
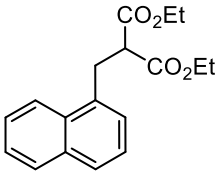
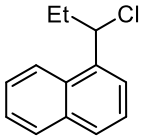
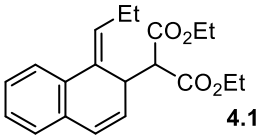
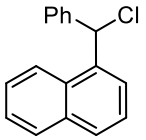
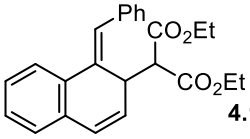
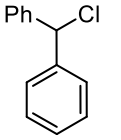
Scheme 4.8

In a later report, Bao and coworkers showed the nucleophilic dearomatization of 1-naphthylmethyl chloride derivatives by malonate nucleophiles under palladium-catalyzed conditions (Table 4.1).[10] Screening of primary (**4.11a**, **4.12a**) and secondary benzyl halides (**4.13a** – **4.15a**) showed that 1,1-diarylmethanes with extended π-conjugation (**4.14a**) highly favor the formation of the dearomatized product **4.14b**, without giving rise to any benzylated product. In addition to malonate nucleophiles various other activated methylenes yielded the ortho substituted dearomatized products in good yields (Scheme 4.9). However, the use of more sterically hindered nucleophiles led to the formation of para-substituted dearomatized products (**4.16**).

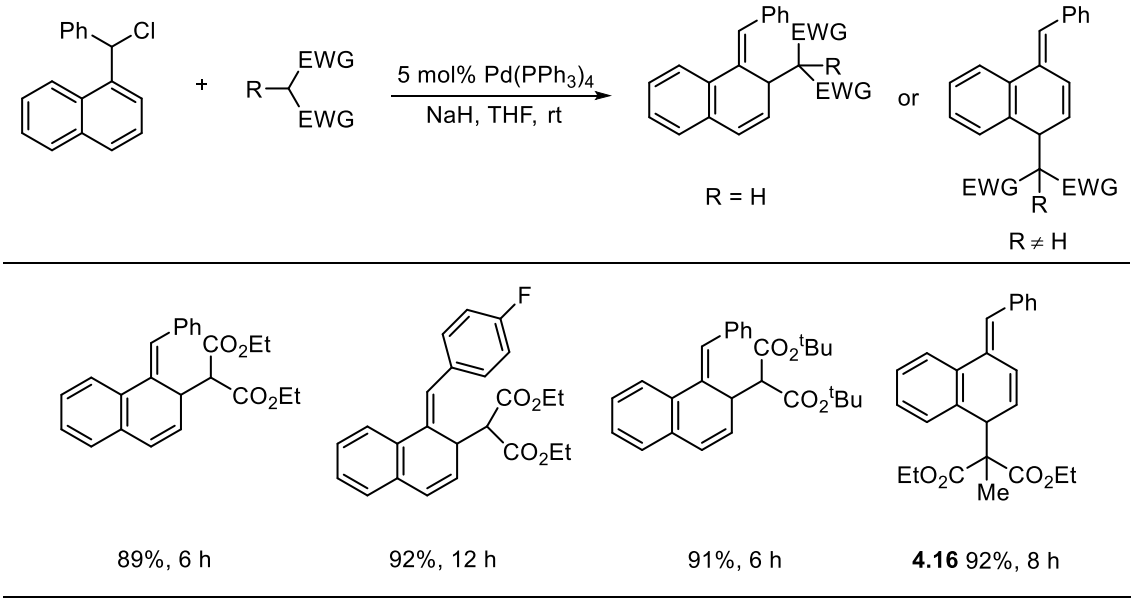
Alternatively, Kuwano has also reported the synthesis of 3-methyl-9,10-dihydrophenanthrenes **4.19**, using an ortho-phenylene tethered to the meta-position of benzyl carbonates **4.17** (Scheme 4.10).[11] Due to geometric constraints, nucleophilic substitution was expected to occur at the ortho-carbon (C3) of Pd-π-benzyl intermediate. However, no products were formed via ortho-substitution. The authors claim that the observed product **4.19** arises from S_N'-type aromatic

substitution and re-aromatization of **4.18** via a 1,5-hydride shift. This is the first report of such an aromatic substitution of a benzylic ester derivative.

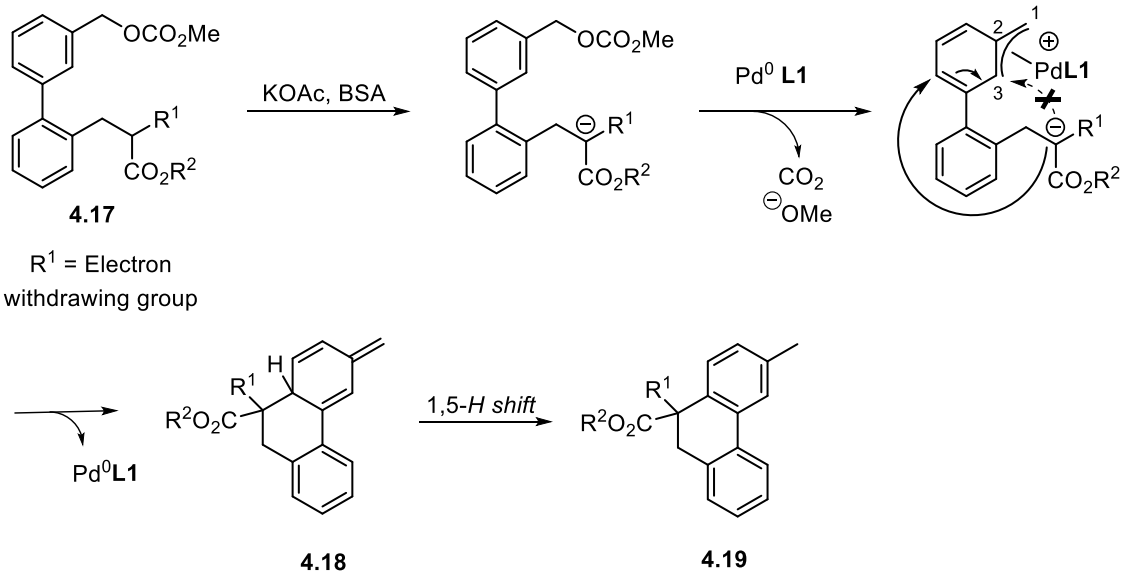
Table 4.1[a]

entry	substrate	product	Yield (%)[b]
1	 **4.11a**	 **4.11b**	64
2	 **4.12a**	 **4.12b**	91
3	 **4.13a**	 **4.13b**	32 (40)[c]
4	 **4.14a**	 **4.14b**	85
5	 **4.15a**		NR[d]

[a]Reaction conditions: Substrates **4.11a - 4.15a** (0.5 mmol), diethyl malonate (0.5 mmol), NaH (1.0 mmol) $Pd(PPh_3)_4$ (5 mol%) in THF (5 mL) at room temperature under N_2.[b]Isolated yield. [c]Yield of the benzylated product, [d]No reaction.



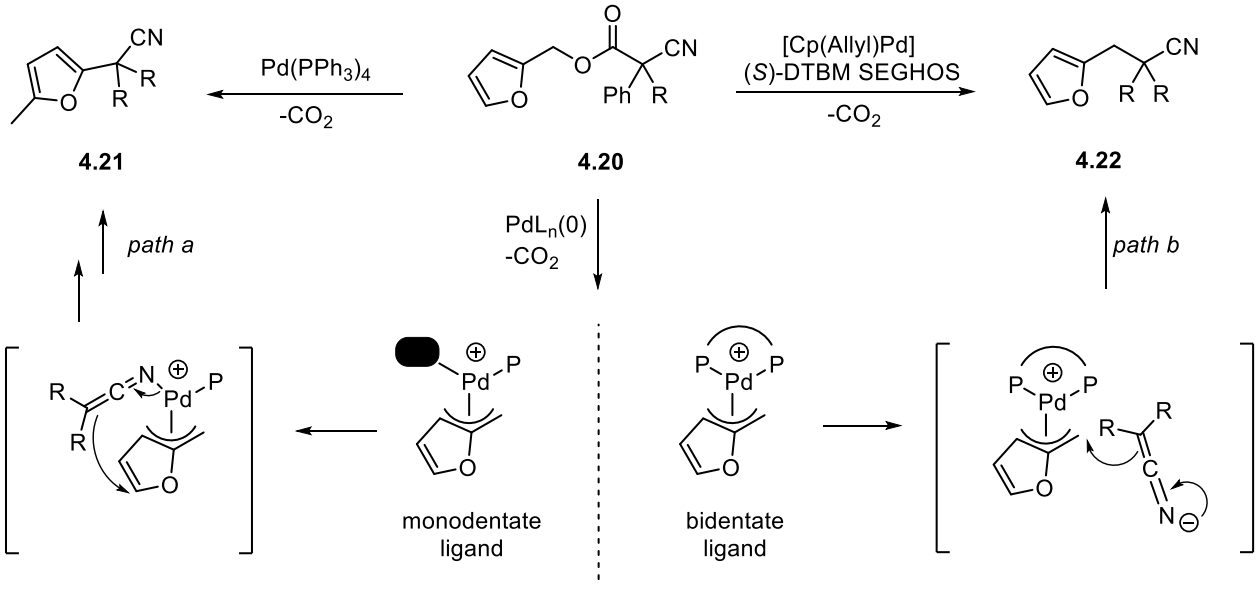
Scheme 4.9



Scheme 4.10

Previously Recio (III), a coworker in the Tunge group, also observed a related reaction that likely arise from a dearomatization-rearomatization sequence. Specifically, Recio observed the

formation of arylated nitriles **4.21** via the decarboxylative coupling of α,α-disubstituted 2-methylfuranyl cyanoacetates (**4.20**) in the presence of $Pd(PPh_3)_4$ (Scheme 4.11).[1b] This was the first arylation reported that proceeds via a catalytic decarboxylative coupling of benzyl electrophiles. Interestingly, changing the catalyst/ligand combination to CpPd(allyl)/(*S*)-DTBM SEGPHOS provided the arylmethylated product (**4.22**). This ligand based selectivity is proposed to arise from a change of mechanism when shifting from a monodentate to a bidentate phosphine ligand. Both reaction paths involve the formation of η^3-palladium-π-furfuryl intermediate, but in the presence of a monodentate ligand (PPh_3) the reaction occurs via an inner-sphere mechanism (path a) due to the access to a vacant coordination site on the metal to result the arylated product **4.21**. However, use of a bidentate ligand [(*S*)-DTBM SEGPHOS] forces the reaction to occur via an outer-sphere mechanism (path b) to yield **4.22,** due to the absence of an open coordination site on the metal.



Scheme 4.11

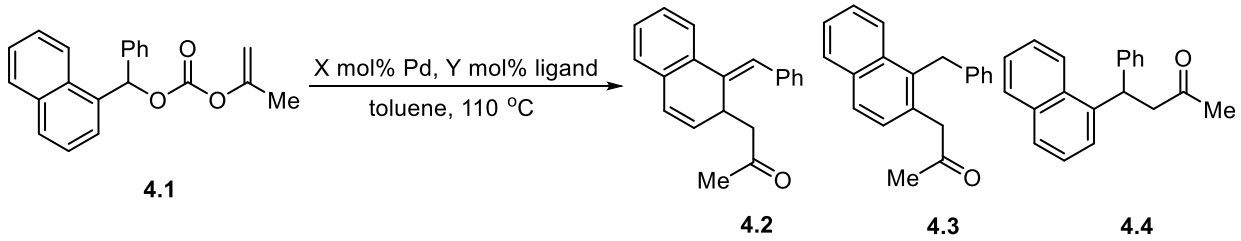
4.1.2 Palladium-catalyzed decarboxylative dearomatization with ketone enolates

Following the initial observation of decarboxylative dearomatization (Scheme 4.2), our efforts were focused on optimizing reaction conditions to obtain the dearomatized ketone product **4.2** in high conversion via the decarboxylative coupling of benzyl enol carbonate **4.1** (Table 4.2, entry 1-10). While, 10 mol% $Pd(PPh_3)_4$ provided both the dearomatized (**4.2**) and arylated ketone (**4.3**) with low conversion, the formation of benzylated ketone **4.4** was not observed (entry 1). The more electron-deficient dba-ligated palladium pre-catalyst with more electron rich tri(2-furyl)phosphine exclusively formed the dearomatized product (entry 5), albeit in very low conversion. Notably, increasing the concentration of the reaction mixture improved conversion of **4.1** to the dearomatized product **4.2** (entry 6). Encouraged by these results different dba-ligated palladium pre-catalysts were screened along with tri(2-furyl)phosphine ligand. To our delight, $Pd(dba)_2$ cleanly converted to the dearomatized product **4.2** in 98% conversion (entry 7). Heating the reaction for a few more hours provided a small amount of isomerization of **4.2** to **4.3** (entry 8). Therefore, the reaction conditions shown in entry 7 were chosen as the optimized reaction conditions for catalytic decarboxylative dearomatization. (Entry 11-14 in Table 4.2 will be discussed in chapter 4.2.2).

With the optimized reaction conditions in hand, the substrate scope was examined (Scheme 4.12). The dearomatized product **4.2** was isolated in 91% yield in *E* configuration. The increased steric hindrance caused by 1-naphthyl and phenyl groups may encourage the observed *E* configuration**.** Substitution at the *para*-position with an alkyl (**4.23**) or halogen (**4.26, 4.27**) moieties provided very good yields. A moderate yield was obtained with the *o*-OMe substrate (**4.24**) which is attributed to the increased steric hindrance. The presence of an inductively electron

withdrawing *m*-OMe also provided the dearomatized product **4.25** in good yield. However, more electron deficient benzyl enol carbonates lowered the yield of the reaction (**4.28-4.30**).

Table 4.2

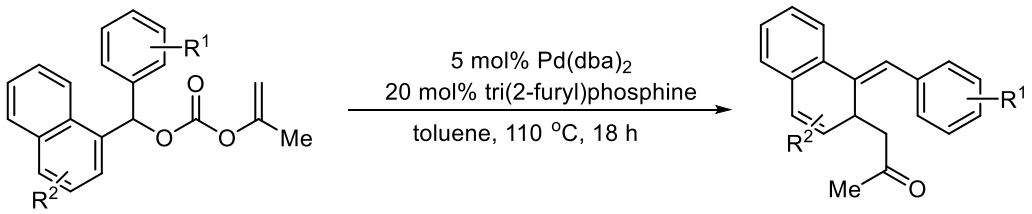


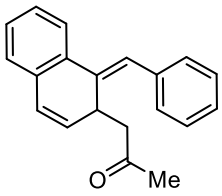
4.1 **4.2** **4.3** **4.4**

entry	X mol%	Pd source	Y mol%	ligand	solvent [concentration][M]	time/ h	% Conv to[a] **4.2 : 4.3 : 4.4**
1	10	$Pd(PPh_3)_4$	-	-	tol [0.04]	18	**23 : 9 : 0**
2	5	Pd_2dba_3	10	dppe	tol [0.04]	18	**20 : 40 : 0**
3	5	Pd_2dba_3	10	(*R*)-SEGPHOS	tol [0.04]	18	**0 : 70 : 21**
4	5	Pd_2dba_3	10	dppp	tol [0.04]	18	**0 : 29 : 0**
5	5	Pd_2dba_3	20	tri(2-furyl)phosphine	tol [0.04]	18	**17 : 0 : 0**
6	5	Pd_2dba_3	20	tri(2-furyl)phosphine	tol [0.1]	18	**40 : 0 : 0**
7	5	$Pd(dba)_2$	20	tri(2-furyl)phosphine	tol [0.2]	18	**98 : 0 : 0**
8	5	$Pd(dba)_2$	20	tri(2-furyl)phosphine	tol [0.2]	24	**95 : 4 : 0**
9	10	$Pd(dmdba)_2$	20	tri(2-furyl)phosphine	tol [0.2]	24	**88 : 0 : 0**
10	10	$Pd_2(dba)_3{\cdot}CHCl_3$	20	tri(2-furyl)phosphine	tol [0.2]	24	**72 : 0 : 0**
11	10	$Pd(PPh_3)_4$	-	-	tol [0.1]	5	**64 : 36 : 0**
12	10	$Pd(PPh_3)_4$	-	-	tol [0.1]	7	**53 : 46 : 0**
13	10	$Pd(PPh_3)_4$	-	-	tol [0.1]	24	**55 : 44: 0**
14	10	$Pd(PPh_3)_4$	-	-	tol [0.2]	24	**11 : 89 : 0**

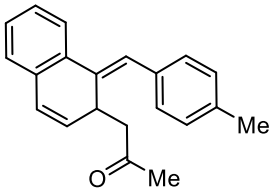
[a] % conv calculated based on ^{1}H NMR.

In addition, a strongly withdrawing *p*-NO_2 substituent did not allow the isolation of dearomatized product and instead delivered the mono-α-arylated product in 57% yield (**4.30**). While all other substrates delivered dearomatized products with ortho substitution, a *p*-Me substituted benzyl carbonate provided the *para*-substituted dearomatized product **4.31** selectively.

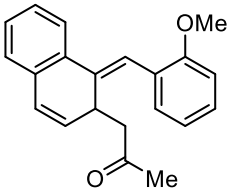




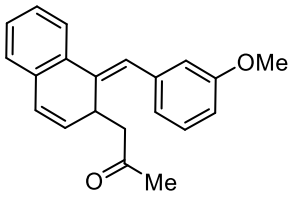
4.2, 91%



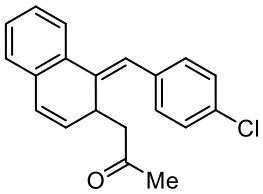
4.23, 82%



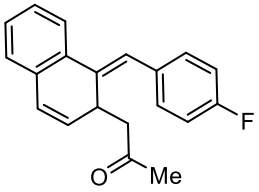
4.24, 63%



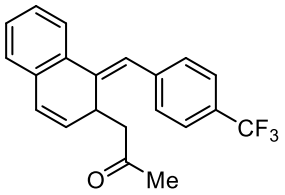
4.25, 86%



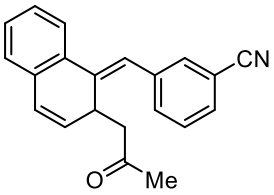
4.26, 83%



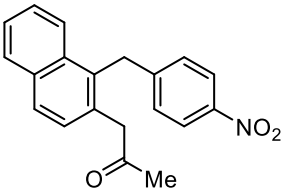
4.27, 86%



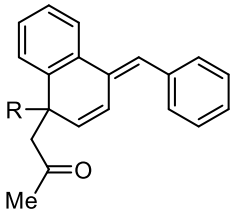
4.28, 48%



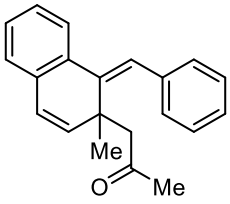
4.29, 59%



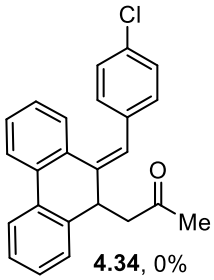
4.30, 57%



4.31, R = Me, 47%
4.32, R = F, 0%



4.33, 0%



4.34, 0%

[a] Yield of isolated product after column chromatography on silica gel. [b] All products were stored in a freezer dissolved in $CHCl_3$.

Scheme 4.12

The formation of *para*-substituted dearomatized product **4.31** can be rationalized as follows (Figure 4.1). A methyl substituent at the para position allows for the generation of a more stabilized cation at the *para*-carbon of η^3-palladium-benzyl intermediate which could favor the formation of *para*-substituted product (**4.31**) instead of the *ortho*-substituted product. Changing the methyl group to a fluoro substituent, did not result the expected product **4.32**, and the unreacted benzyl enol carbonate was isolated to account for the mass-balance.

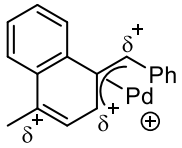
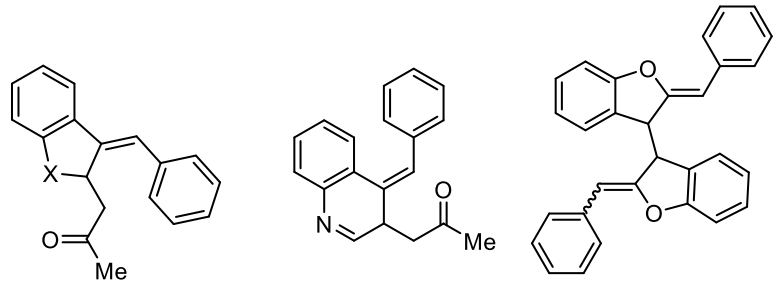


Figure 4.1

Similar to previous observations (Scheme 3.10), a 2-Me group on the naphthyl moiety (**4.33**) did not result any product, presumably due to the steric hindrance preventing the formation of the requisite Pd-π-benzyl intermediate. Unfortunately, efforts to extend the electrophile scope to phenanthrene derivatives were unsuccessful (**4.34**), due to the formation of a complex reaction mixture, which could not be purified.

Further expansion of the substrate scope to hetereoaromatic moieties was met with limited success. Although **4.35** was isolated in 63% yield, changing to an indole (**4.36**) or quinoline (**4.37**), did not result in any product. Interestingly, with a benzofuran moiety, the expected product was not formed. Instead, the formation of **4.38** was observed as a 1:1 mixture of isomers in 76% yield. The formation of **4.38** could occur from an initial ligand exchange and reductive elimination process (Scheme 4.13).

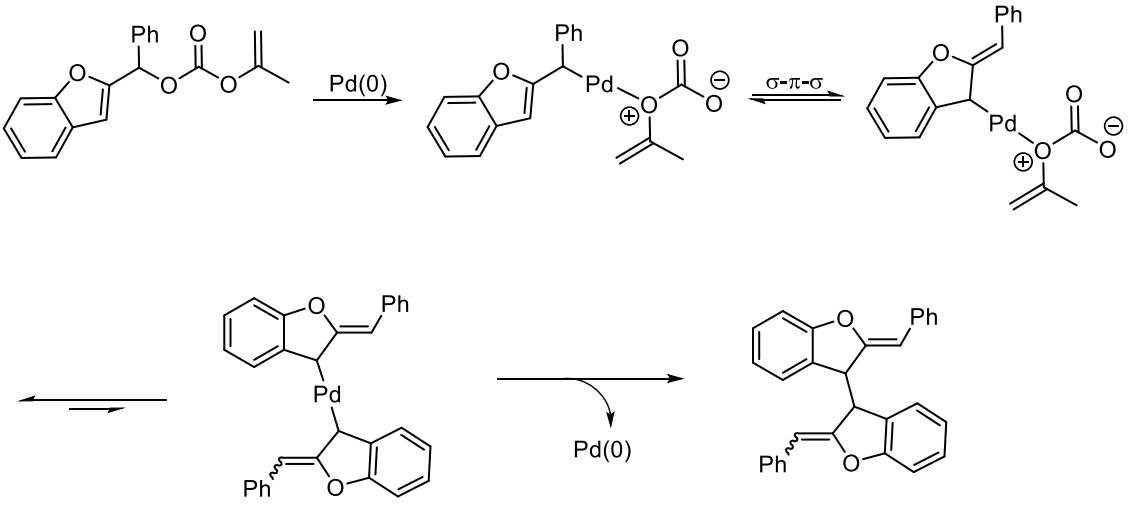


4.35, X = S, 63%
4.36, X = NBoc, 0%[a]

4.37, NR

4.38, 76%, 1:1

[a] Did not result a clean conversion.



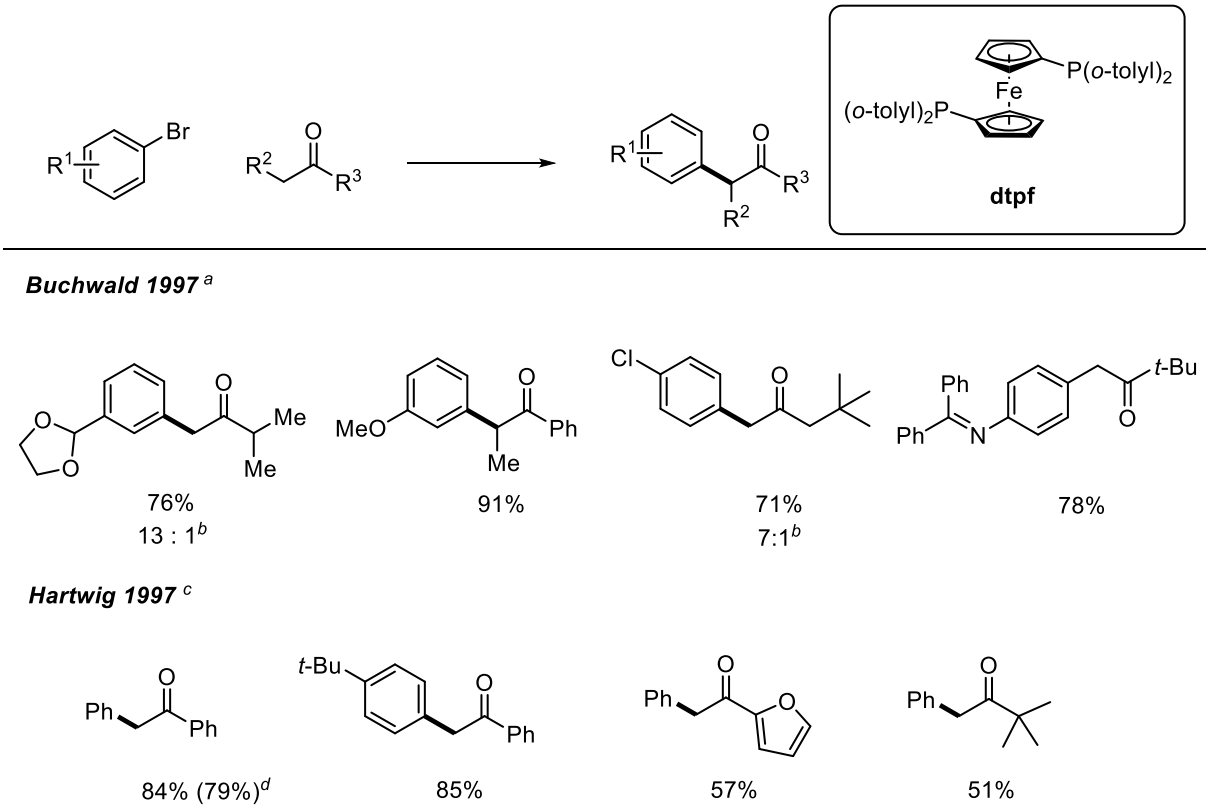
Scheme 4.13

Notably, the isolated dearomatized products (Scheme 4.12) are stable on a silica column, and these were purified using flash chromatography. We also noted the high stability of these dearomatized compounds in $CDCl_3$ similar to Yamamoto's report.[6] In solution in an NMR tube, these dearomatized compounds were stable for weeks at room temperature. Therefore, these compounds were stored long-term in a freezer as solutions in $CHCl_3$. After months, we observed the decomposition of these products, but we did not observe a significant isomerization to the arylated products.

4.2 Palladium-catalyzed arylation of ketone enolates

4.2.1 Introduction

Arylation of ketone enolates via transition metal catalyzed cross-coupling reactions has attracted considerable attention during the last decade. In 1997, Buchwald and Hartwig independently reported the arylation of ketones via the direct coupling of aryl halides with ketones in the presence of a base and a palladium catalyst (Scheme 4.14).[12]

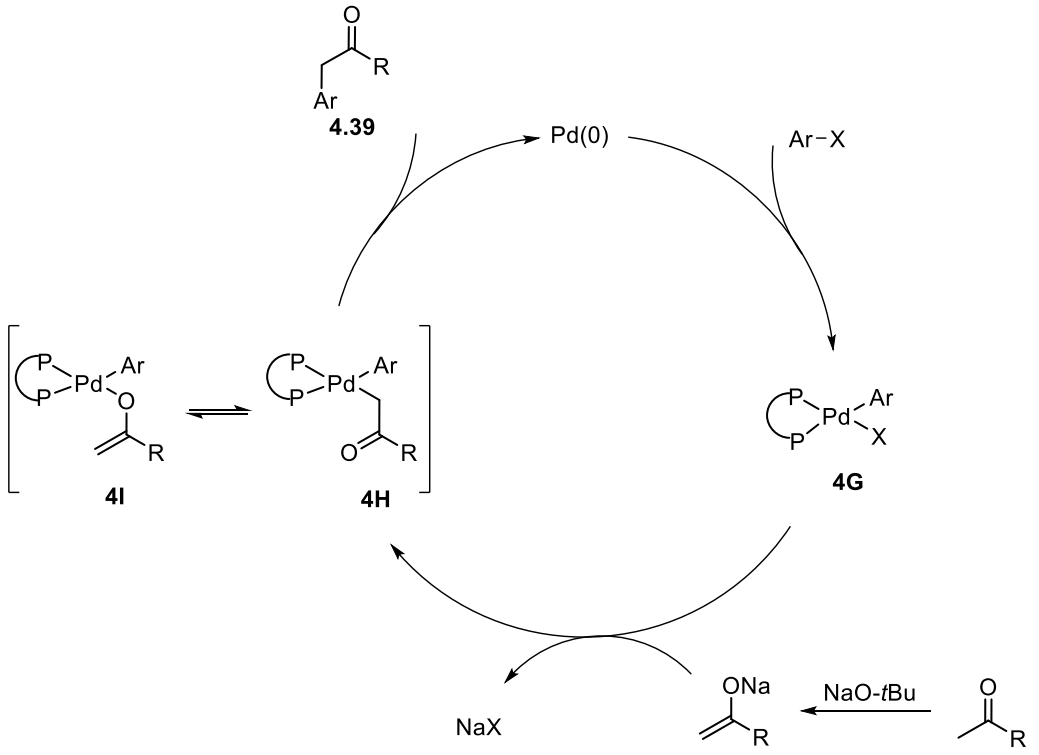


a1.5 mol % of $Pd_2(dba)_3$, 3.6 mol % of BINAP or Tol-BINAP, 1.3 equiv of NaO*t*-Bu, THF, 70 °C, 4 - 12 h. bmonoarylation : diarylation ratio. c7.5 mol % $Pd(dba)_2$, 9 mol% dtpf or dppf, 2.2 equiv of $KN(SiMe_3)_2$, refluxing THF, 0.75 h. dThe yield obtained using aryl iodide as the coupling partner.

Scheme 4.14

In the method reported by Buchwald, the coupling of aryl bromides to ketones was carried out in the presence of $Pd_2(dba)_3$, BINAP (or tol-BINAP) and NaO*t*-Bu,[12a] while, Hartwig used $Pd(dba)_2$, dppf (or dtpf) and $KN(SiMe_3)_2$ or NaO*t*-Bu.[12b] Prior to these reports, arylation of ketones required the preformation of tin, bismuth or silyl enolates.[13]

A generalized mechanism for the base mediated palladium-catalyzed arylation of ketones is shown in Scheme 4.15. In the reaction mechanism, the oxidative addition of aryl halide to Pd(0), generates the adduct **4G** which undergoes transmetalation with the sodium enolate to generate **4H** and **4I**. The arylated ketone **4.39** will be generated via the reductive elimination of **4H** or **4I**.

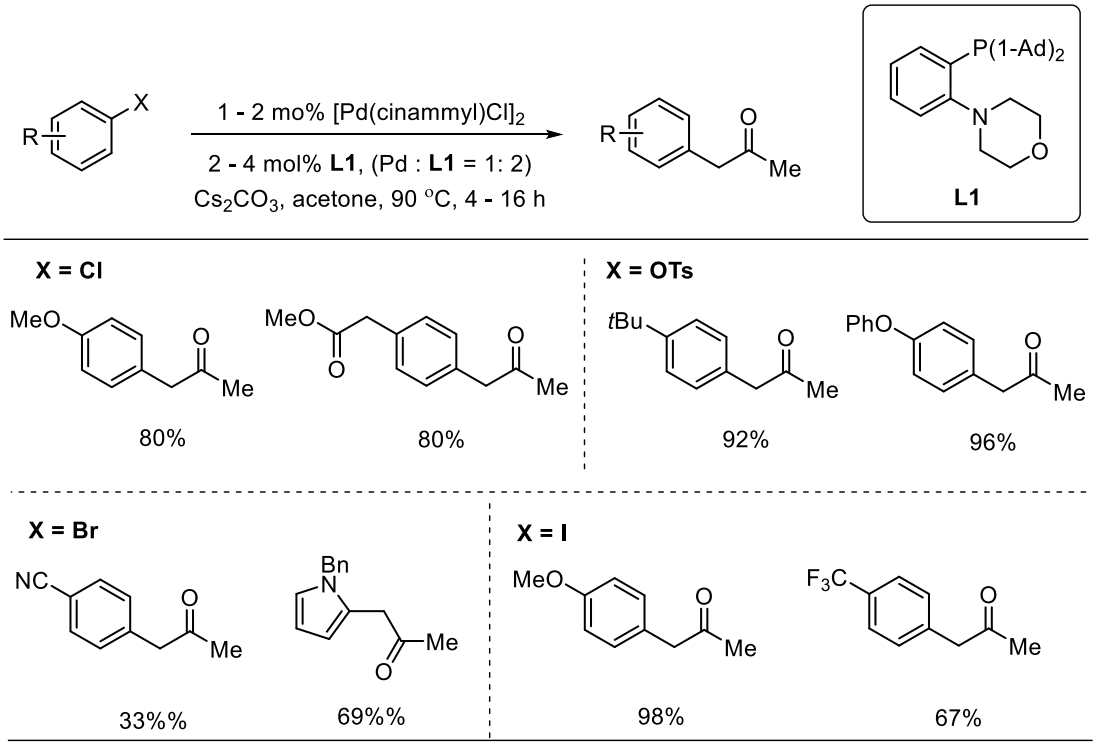


Scheme 4.15

The literature reported methods for α-arylation of ketones are mostly limited to alkyl aryl ketones and dialkyl ketones that have a steric bias, for which the formation of enolate is highly

controlled.[12, 14] Additionally, with some substrates diarylation could not be avoided (Scheme 4.14).[12a]

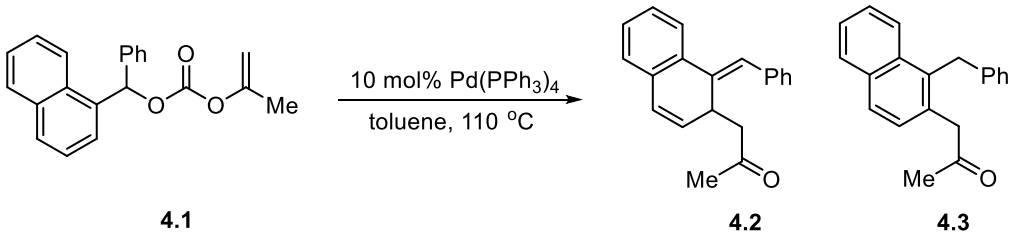
Similar arylations with acetone or dialkyl ketones with two enolizable positions is scarcely reported in literature.[15] Direct mono-α-arylation of acetone with an aryl halide is undoubtedly challenging, due to the presence of several acidic C-H bonds that are prone to undergo enolate formation in the presence of base, because, the increased acidity of benzylic C–H's of the mono-α-arylated acetone product can easily lead to the formation of the α,α-diarylated products. Therefore, in general, acetone equivalents such as stannyl or silyl enolates of acetone were used for the arylation of acetone until Stradiotto reported the mono-α-arylation of acetone with aryl halides and tosylates (Scheme 4.16).[15c, 16]



Scheme 4.16

4.2.2 Palladium-catalyzed decarboxylative arylation of ketone enolates

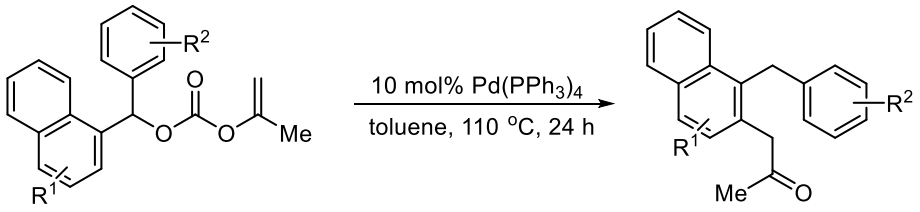
Given the high synthetic interest for α-arylation of acetones, we next focused on developing a palladium-catalyzed decarboxylative route for the α-arylation of acetones/ketones via the rapid isomerization of the dearomatized ketones. As previously shown, the formation of the mono-α-arylated ketone was observed upon prolonged heating with 10 mol% $Pd(PPh_3)_4$ (entry 11-13, Table 4.2). When the concentration of **4.1** was increased, the mono-α-arylated product **4.3** was formed in a satisfactory ratio of **4.2**:**4.3** = 11:89 (entry 14, Table 4.2), and **4.3** was isolated in 74% yield (Scheme 4.18).

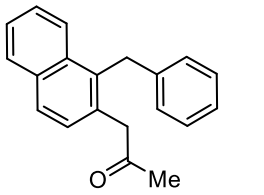


4.1 **4.2** **4.3**

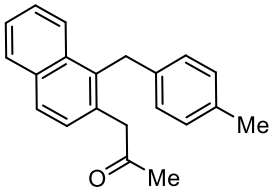
Scheme 4.17

Using the reaction conditions in entry 14, Table 4.2, the substrate scope was then examined (Scheme 4.18). Remarkably, for the substrates **4.40**-**4.47**, after 24 hours of reaction no dearomatized ketones were detected; the initially generated dearomatized products were fully isomerized to the mono-α-arylated products without giving rise to any poly-arylated products. Unreacted starting material accounted for the mass balance of these arylation reactions. Chloro and fluoro substituted benzyl enol carbonates also provided the arylated products (**4.43** and **4.44**) in excellent yields.

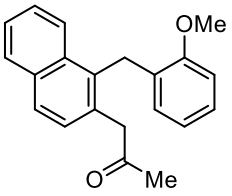




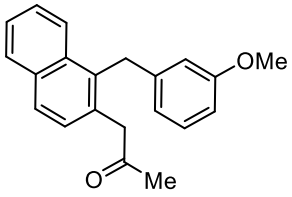
4.3, 74%
(**4.3**:**4.2** = 8:1)



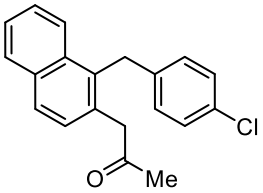
4.40, 66%



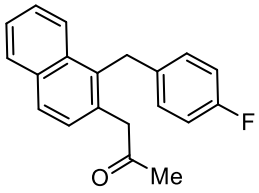
4.41, 57%



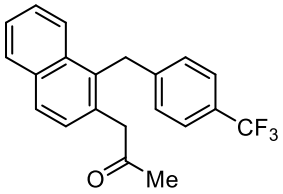
4.42, 90%



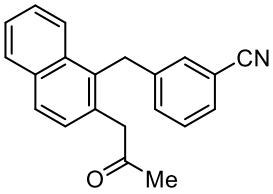
4.43, 92%



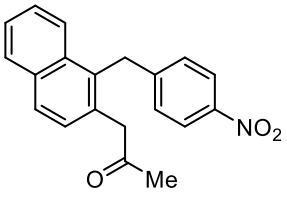
4.44, 93%



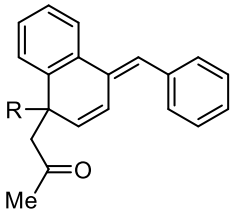
4.45, 16%



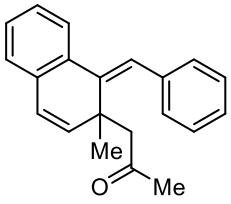
4.46, 73%



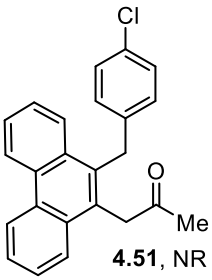
4.47, 74%



4.48, R = Me, 74%
4.49, R = F, NR



4.50, NR



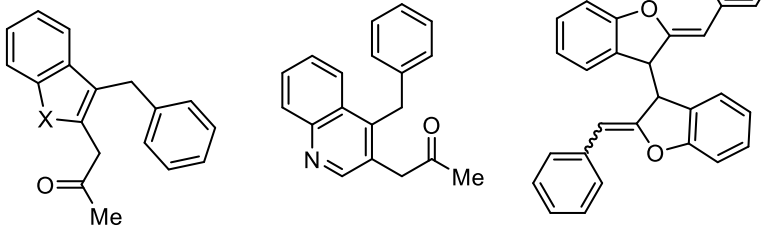
4.51, NR

[a]Yield of isolated product after column chromatography on silica gel.

Scheme 4.18

Notably, electron deficient benzyl enol carbonates with a *m*-CN or a *p*-NO_2 substituent provided the arylated products **4.46** and **4.47** in good yields. This was a very distinct result compared to decarboxylative benzylation of alkynes, in which electron deficient 1,1-diarylmethane carboxylic acid derivatives were either less reactive or completely unreactive (Chapter 3). As expected, **4.48** was isolated as the dearomatized ketone as it is unable to undergo re-aromatization via proton transfer or hydride shift. With the fluoro substituent at the 4-position (**4.49**) no reaction was observed and the unreacted benzyl enol carbonate was present in the NMR spectrum of the crude reaction mixture. Similar to previous observations (Scheme 3.10 and 4.12) **4.50 a**nd **4.51** were not formed under our standard reaction conditions.

Unfortunately, under the optimized conditions enol carbonates with heteroaromatic moieties did not undergo a clean conversion to provide the expected products (**4.52**-**4.55**). However, the reactivity of benzofuran enol carbonate was similar to before, in which **4.55** was isolated as a 1:2 mixture of isomers in 50% yield.



4.52 X = S, 0%[a]
4.53 X = NBoc, 0%[a]

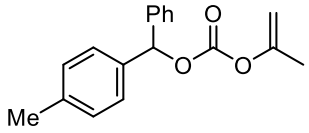
4.54, NR

4.55, 50% (1:2)

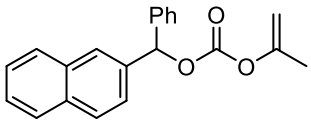
[a]Did not result a clean conversion.

The reactivity of benzyl enol carbonates **4.56** and **4.57** were also briefly evaluated for dearomatization and arylation reactions. While **4.56** did not show any reactivity, **4.57** produced a

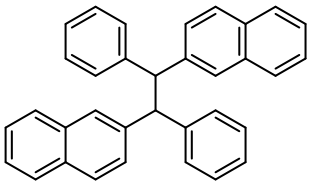
complex mixture of products from which **4.58** was isolated and characterized. The formation of **4.58** could occur via a mechanism similar to Scheme 4.13.



4.56

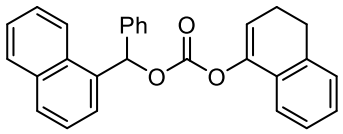


4.57

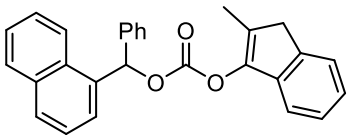


4.58

To further expand the substrate scope of the nucleophilic coupling partner, cyclic as well as other acyclic benzylic enol carbonates were synthesized. Under the optimized reaction conditions cyclic benzyl enol carbonates **4.59** and **4.60** did not provide the expected product even in moderate selectivity.

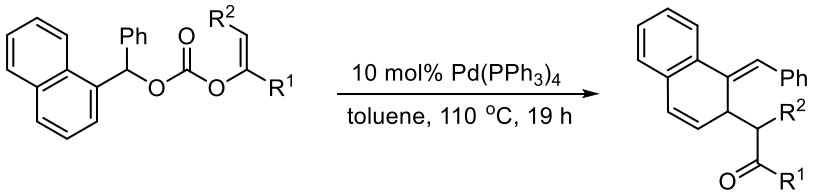


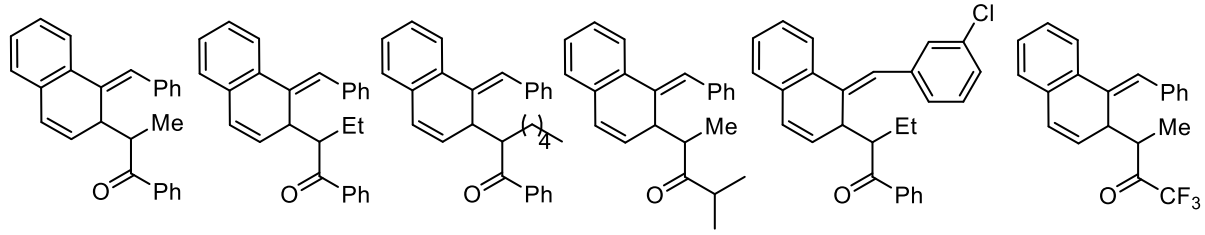
4.59



4.60

Then we turned our attention to other acyclic enolates. With 5 mol% $Pd(dba)_2$ and 20 mol% tri(2-furyl)phosphine the decarboxylative coupling reactions of acyclic enolates were sluggish. When the catalyst was changed to $Pd(PPh_3)_4$ (10 mol%), benzylic enol carbonates were cleanly converted to the respective dearomatized products, without giving rise to any arylated ketones (Scheme 4.19). The products **4.61**-**4.65** were obtained in good yields, albeit with poor diastereoselectivity. Protonated enolates accounted for the mass balance of these reactions. Unfortunately, attempts to couple a trifluoromethyl ketone (**4.66**) resulted in no conversion.



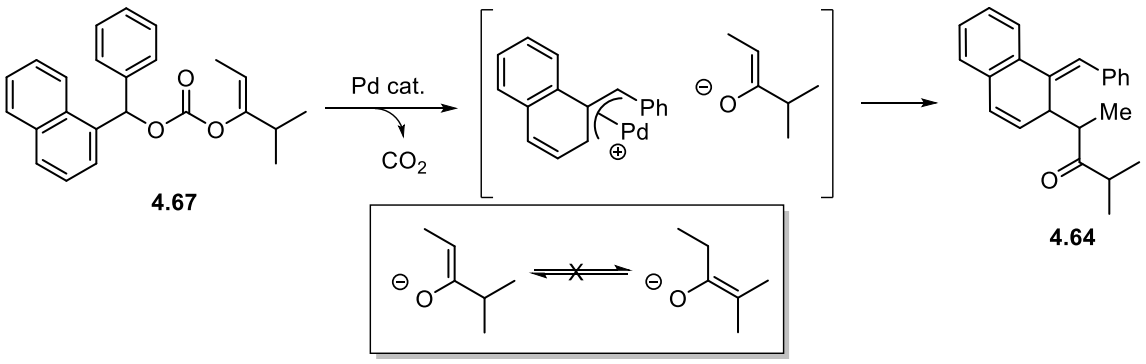


4.61, 86% dr 1 : 1.3	**4.62**, 81% dr 1 : 1.1	**4.63**, 72% dr 1 : 1.1	**4.64**, 88% dr 1 : 1.4	**4.65** 73% dr 1 : 1.5	**4.66**, NR

[a]Yield of isolated product after column chromatography on silica gel. [b]Diastereomeric ratio (dr) was determined by ^{1}H NMR.

Scheme 4.19

It is also noteworthy that benzyl enol carbonate **4.67** cleanly provided **4.64** without any side-products resulting from enolate isomerization (Scheme 4.20). Unfortunately, prolonged heating did not provide the arylated product with any of these substrates (**4.61**-**4.65**). While the exact reason for this is unclear, it is thought the increased steric hindrance at the α-C slows down the rate of isomerization to the arylated ketone.

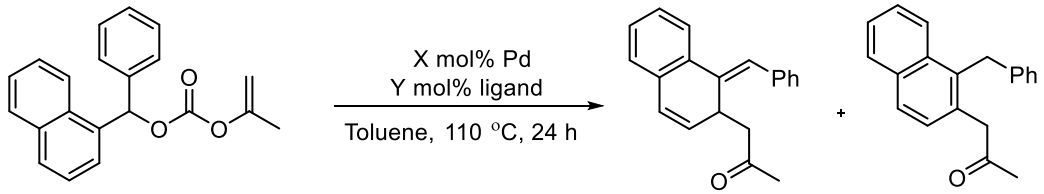


Scheme 4.20

Next, additional experiments were performed in order to gain mechanistic insight into the isomerization of the dearomatized ketones to the mono-α-arylated ketones under $Pd(PPh_3)_4$ catalyzed conditions. The ^1H NMR spectral data of the decarboxylative coupling of **4.1** under optimized conditions for the two protocols (dearomatization and arylation) are shown in Table 4.3. After isolation, **4.2** was subjected to the identical reaction conditions but in the absence of any catalyst/ligand (entry 1 in Table 4.4), the dearomatized ketone **4.2** did not undergo significant isomerization (**4.2**:**4.3** is 33:1). However, in the presence of 10 mol% $Pd(PPh_3)_4$ a 1:1 ratio of **4.2**:**4.3** was observed (entry 2, Table 4.4). Therefore, the isomerization of **4.2** to **4.3** is a palladium-catalyzed process.

The slower rate of isomerization of **4.2** in the presence of $Pd(PPh_3)_4$ compared to entry 2 in Table 4.3 led us to propose of the potential additional involvement of a Pd(II) species in the isomerization pathway. To test this hypothesis, the palladium source was changed to $Pd(OAc)_2$, which resulted **4.2**:**4.3** in a 2.5:1 ratio (entry 3, Table 4.4). Therefore, both Pd(0) and Pd(II) species can effect the isomerization of **4.2** to **4.3**.

Table 4.3

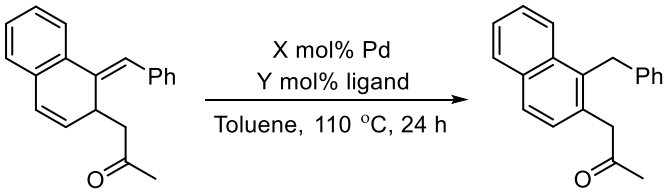


4.1 **4.2** **4.3**

entry	X mol%	Pd scource	Y mol%	ligand	**4.2** : **4.3**[a]
1	5	$Pd(dba)_2$	20	tri(2-furyl)phosphine	20 : 1
2	10	$Pd(PPh_3)_4$	–	–	1 : 8

[a]The ratio of **4.2:4.3** was calculated using ^1H NMR.

Table 4.4

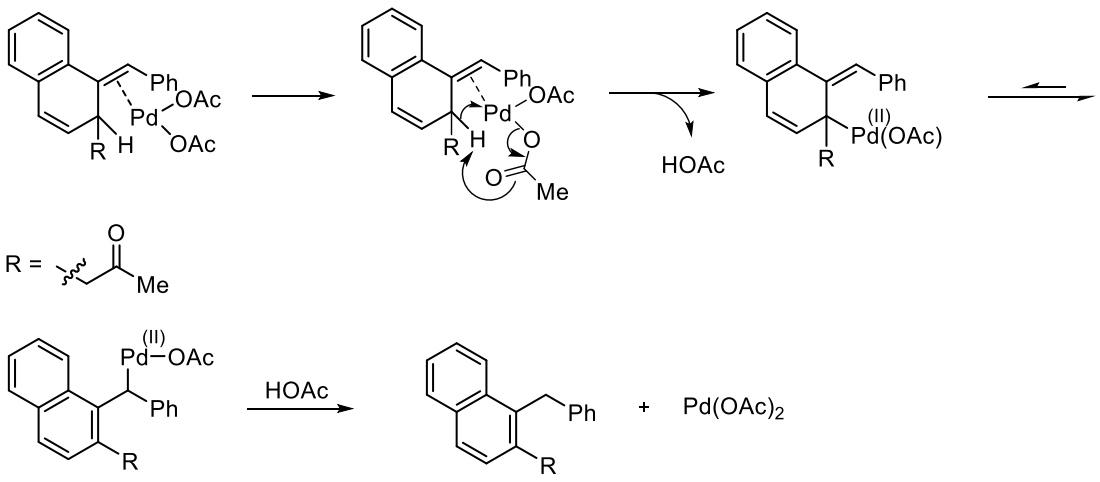


4.2 **4.3**

entry	X mol%	Pd scource	Y mol%	ligand	**4.2**:**4.3**[a]
1	–	–	–	–	33:1
2	10	$Pd(PPh_3)_4$	–	–	1:1
3	5	$Pd(OAc)_2$	–	–	2.5:1
4	5	$Pd(dba)_2$	20	tri(2-furyl)phosphine	6:1
5	5	$Pd(dba)_2$	20	PPh_3	3:1

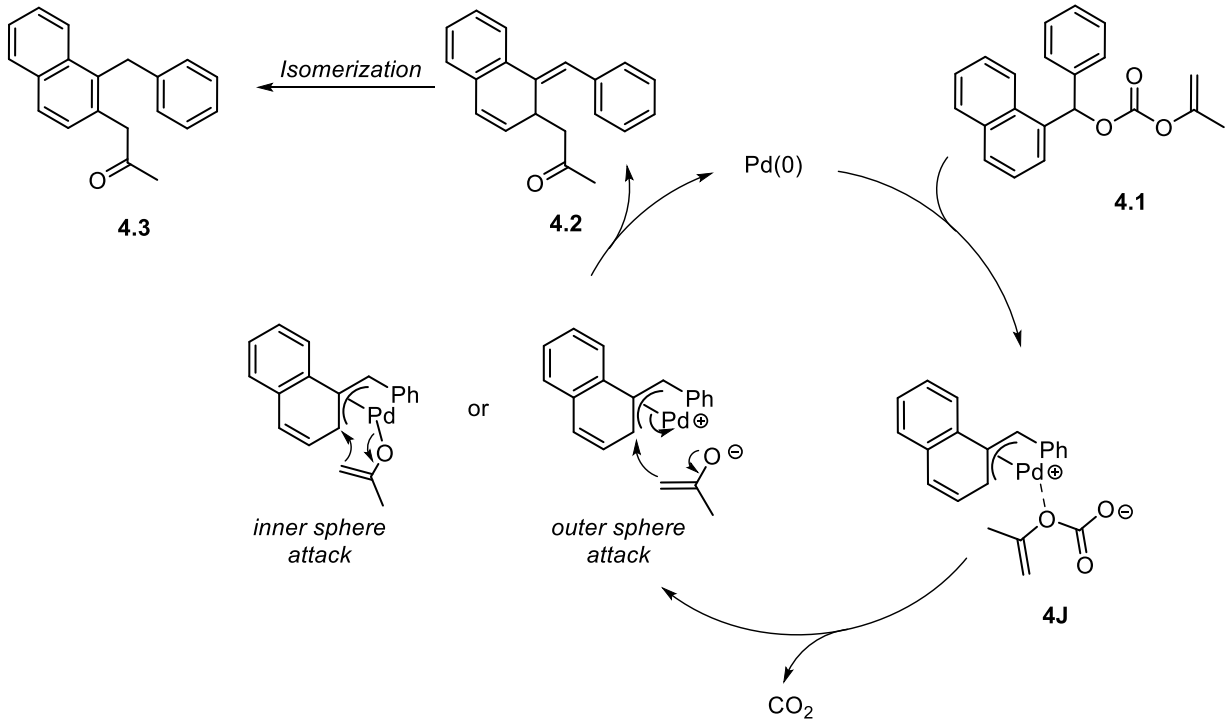
[a]The ratio of **4.2**:**4.3** was calculated by ^{1}H NMR.

Interestingly, with $Pd(dba)_2$ and tri(2-furyl)phosphine the isomerization occurred in a significantly lower rate (**4.2**:**4.3** = 6:1, entry 4, Table 4.4). The influence of the electron rich tri(2-furyl)phosphine on the rate of isomerization was studied by changing the ligand to PPh_3 (entry 5). In the presence of PPh_3 the isomerization rate was significantly faster compared to that of entry 4, showing the contribution of electron rich tri(2-furyl)phosphine to lowering the rate of isomerization. Moreover, comparison of entries 2 and 5 in table 4.4, shows the involvement of dba in slowing down the rate of isomerization, thus demonstrating catalyst selectivity. While an exact mechanism for the isomerization is not clear, a plausible mechanism for the $Pd(OAc)_2$ catalyzed isomerization is given in Scheme 4.21.



Scheme 4.21

A likely catalytic cycle for the decarboxylative dearomatization is shown in Scheme 4.22. In the reaction mechanism, the Pd-π-benzyl carboxylate intermediate (**4J**) is generated upon oxidative addition of benzyl enol carbonate (**4.1**) to Pd(0).[17]

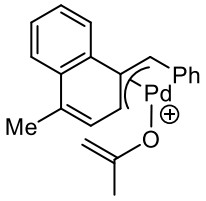


Scheme 4.22

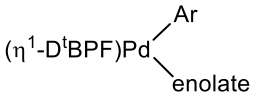
Decarboxylation of **4J** generates the enolate anion *in situ*, which could react with Pd-π-benzyl intermediate via an inner sphere or an outer sphere mechanism to deliver the product **4.2**.

The formation of **4.2** with bidentate ligands [e.g. dppe, (*R*)-SEGPHOS and dppp, entry 2-4 in Table 4.2], and formation of *p*-substituted ketone **4.31** and **4.48**,[11] suggest an outer sphere pathway for the catalytic cycle although not conclusively.

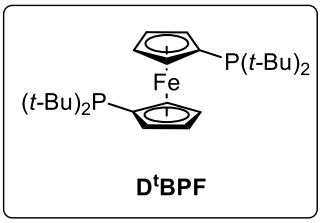
An inner sphere mechanism is also equally viable for several reasons. The observed regioselectivity was remarkable in dearomatization/arylation without generating any products via the generally favored benzylation pathway. Moreover, the formation of *para*-substituted arylated ketone could result from a **4K**-type intermediate.[1b, 7] In addition, experimentally Hartwig *et al*., has shown the formation of **4L**-type intermediate in the catalytic arylation with bisphosphine ligands, in which bisphosphine ligand is bound to palladium via η^1 coordination due to increased steric hindrance.[18]



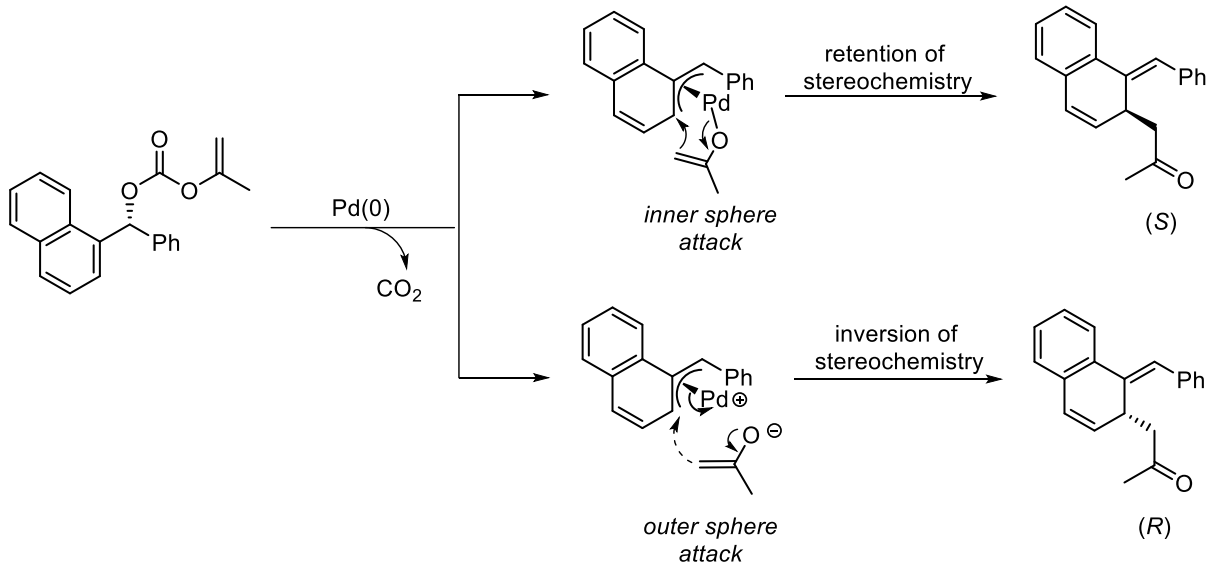
4K



4L

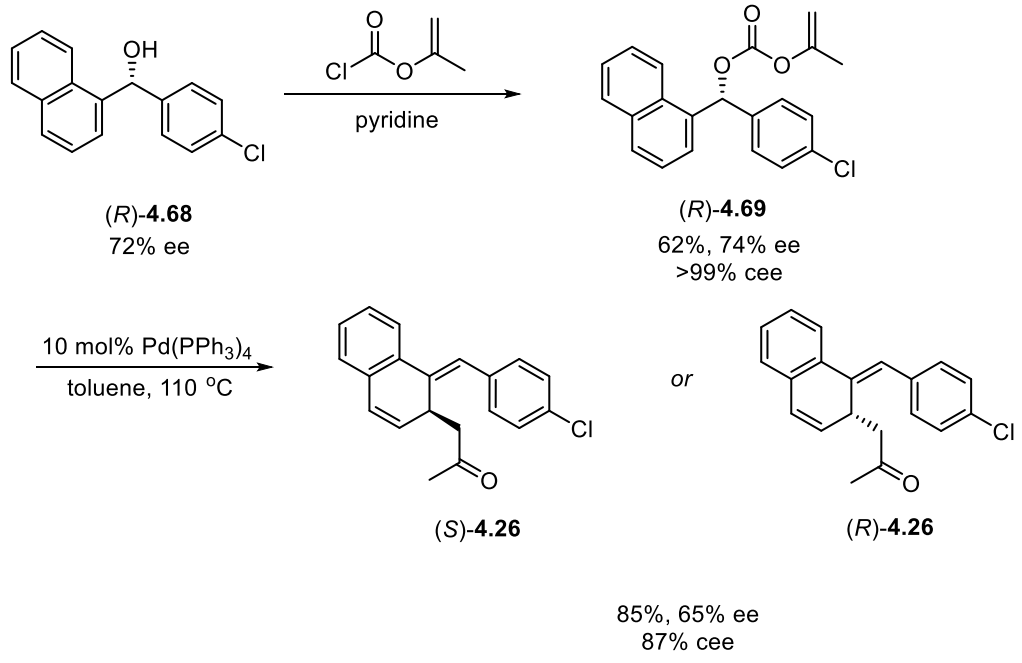


In order to gain insight in to the reaction mechanism, a stereochemical study was conducted using enantioenriched benzyl enol carbonates. While an inner sphere attack of the enolate would result the product with retention of configuration, an outer sphere attack of the enolate would deliver the product with inversion (Scheme 4.23).



Scheme 4.23

The enantioenriched benzyl enol carbonate (*R*)-**4.69** was synthesized from the respective enantioenriched diarylmethanol (*R*)-**4.68**. Under optimized reaction conditions (*R*)-**4.69** provided the dearomatized product **4.26** in 85% yield and 87% cee (Scheme 4.24). This initial result demonstrated that the decarboxylative dearomatization is stereospecific.



Scheme 4.24

Efforts were then directed to obtain an x-ray crystal structure of **4.26,** in order to determine the absolute configuration of the *ortho*-carbon of the 1-naphthyl moiety. Unfortunately, all attempts to obtain an x-ray crystal structure of **4.26** were unsuccessful. The summer 2015 REU student Jordie Compton is currently working on synthesizing dearomatized ketone products with different substituents on the aryl moiety, in order to obtain an x-ray crystal structure, thereby to elucidate the reaction mechanism.

In summary, we developed two protocols via the decarboxylative coupling of diaryl enol carbonates. While $Pd(dba)_2$ with tri(2-furyl)phosphine efficiently delivers the dearomatized ketone coupling products, $Pd(PPh_3)_4$ rapidly promotes isomerization of the dearomatized ketones to the arylated ketone products. A major limitation is that these methods require the use of benzyl enol carbonates having a 1-naphthyl moiety. Efforts to extend these methods to other aromatic and heteroaromatic systems was met with very limited success.

References

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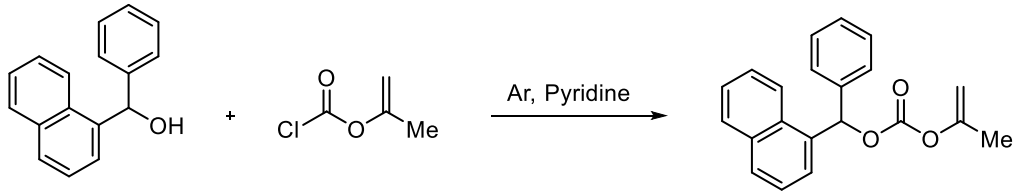
Appendix A3

General Information:

All reactions were run under an argon atmosphere using standard Schlenk techniques or an inert atmosphere glove box. All glassware were oven or flame dried prior to use. All palladium catalysts and ligands were purchased from Strem and stored in the glove box under an argon atmosphere. Toluene and THF were dried over sodium and distilled in the presence of benzophenone. Dried toluene was taken to the glove box in a Schlenk flask with activated molecular sieves. CH_2Cl_2 was dried over alumina. Other commercially available solvents were used without additional purification. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity silica obtained from Sorbent Technologies.

^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer equipped with a QNP cryoprobe and referenced to residual protio solvent signals. Structural assignments were based on ^1H, ^{13}C, DEPT-135, COSY, NOESY and HSQC. Mass spectrometry was run using EI or ESI techniques.

Representative procedure for the synthesis of benzyl vinyl carbonates:

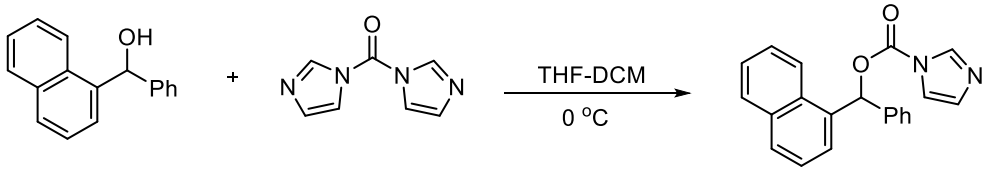


A flask with a stir bar was charged with benzyl alcohol (500 mg, 2.1 mmol) and pyridine (0.50 mL, 6.3 mmol). This was cooled in an ice bath for 30 minutes. Isopropenyl chloroformate (0.27

mL, 2.6 mmol) was added dropwise to the reaction mixture and left for overnight stirring with gradual warming to room temperature. The resulting mixture was quenched with 2M HCl and extracted with diethyl ether. Combined organics were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo.* The crude mixture was purified by flash chromatography.

General procedure for the synthesis of naphthalen-1-yl(phenyl)methyl 1*H*-imidazole-1-carboxylate:

Followed the general procedure reported by Trost by replacing the allyl alcohol with benzyl alcohol.[1]

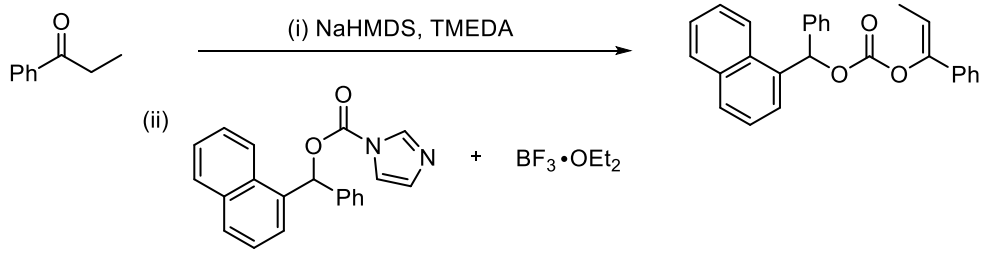


Representative procedure for the synthesis cyclic benzyl vinyl carbonates:

Followed the procedure in the Trost report, however, benzyl alcohol was used instead of allyl alcohol.[1]

Representative procedure for the synthesis acyclic (*Z*)-benzyl vinyl carbonates:

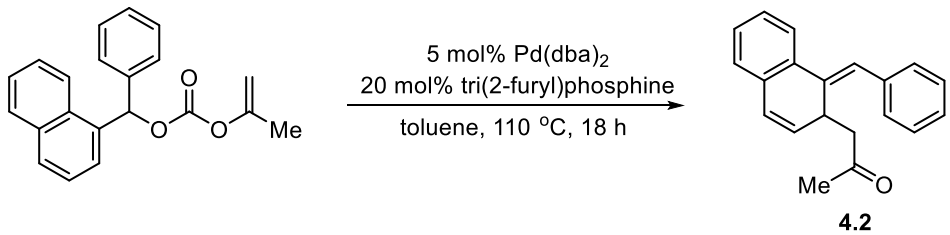
A slightly modified procedure was followed to that reported by Trost.[1]



In a glove box, a clean 100 mL Schlenk flask with a stir bar was charged with hexamethyldisilazane sodium salt (NaHMDS) (366 mg, 2 mmol). The Schlenk flask was sealed with a septum, and taken out of the glove box. Then the flask was cooled in a dry ice/acetone bath for 5 min, and dry THF (7 mL) was transferred slowly. The flask was warmed to 0 °C to make a clear solution, and TMEDA (0.29 mL, 2 mmol) was added. The flask was again placed in the dry ice/acetone bath, and a solution of propiophenone (0.22 mL, 1.6 mmol) in THF (1.6 mL) was added slowly to the reaction mixture over 3 minutes. This reaction mixture was allowed to stir for 1 hour. A separate flask was charged with benzyl 1*H*-imidazole-1-carboxylate (656.7 mg, 2 mmol) and THF (1.6 mL) and this was cooled to -78 °C. Upon cooling $BF_3.OEt_2$ (0.24 mL, 2 mmol) was added to the 1*H*-imidazole-1-carboxylate, and this was stirred for 15 minutes. After 1 hour benzyl 1*H*-imidazole-1-carboxylate and $BF_3.OEt_2$ solution was transferred to the enolate mixture via a cannula and the reaction mixture was stirred overnight. The resulting reaction mixture was quenched with NH_4Cl and extracted with diethyl ether. The combined organics were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crude mixture was purified by flash chromatography with 2% diethyl ether in petroleum ether.

All the synthesized benzyl vinyl carbonates cleanly provided a single isomer. From 2D-NMR studies it was confirmed that this method provides *Z*-benzyl vinyl carbonates.

Representative procedure for the Pd-catalyzed decarboxylative dearomatization:

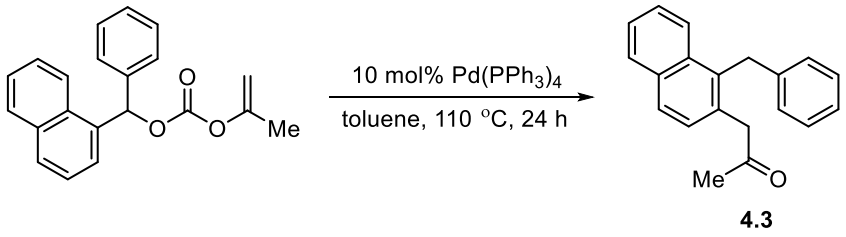


4.2

In a glove box, under an argon atmosphere, a flame dried 10 mL microwave vial with a stir bar was charged with benzyl vinyl carbonate (100 mg, 0.31 mmol), $Pd(dba)_2$ (9 mg, 0.016 mmol), tri(2-furyl)phosphine (14.6 mg, 0.063 mmol) and toluene (1.6 mL). The Schlenk tube was equipped with a septum and the sealed tube was removed from the glove box and stirred at 110 °C for 18 hours. The resulting reaction mixture was cooled to room temperature and concentrated *in vacuo* and was purified via flash chromatography over silica gel. The isolated compound **4.2** was stored in the fridge dissolved in chloroform.

(From 1D and 2D NMR data the product was conformed as the *E*-isomer)

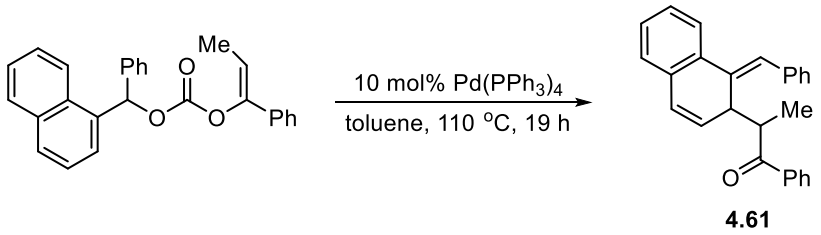
Representative procedure for the Pd-catalyzed decarboxylative arylation:



4.3

In a glove box, under an argon atmosphere, a flame dried 10 mL microwave vial equipped with a stir bar was charged with benzyl vinyl carbonate (80 mg, 0.25 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and toluene (1.3 mL). The Schlenk tube was equipped with a septum and the sealed tube was removed from the glove box and stirred at 110 °C for 24 hours. The resulting reaction mixture was cooled to room temperature and concentrated *in vacuo* and was purified via flash chromatography over silica gel to isolate **4.3**.

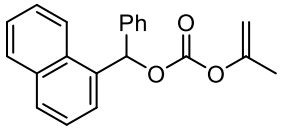
Representative procedure for the Pd-catalyzed decarboxylative dearomatization:



4.61

In a glove box, under an argon atmosphere, a flame dried 10 mL microwave vial was charged with (*Z*)-benzyl vinyl carbonate (64 mg, 0.16 mmol), $Pd(PPh_3)_4$ (18.7 mg, 0.016 mmol), and toluene (0.8 mL). The Schlenk tube was equipped with a septum and the sealed tube was removed from the glove box and stirred at 110 °C for 19 hours. The resulting reaction mixture was cooled to room temperature and concentrated *in vacuo* and was purified via flash chromatography over silica gel to afford **4.61**.

Characterization data for benzyl vinyl carbonates:



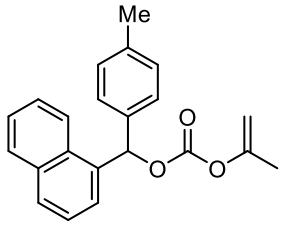
naphthalen-1-yl(phenyl)methyl prop-1-en-2-yl carbonate (SM-4-164)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.96 (m, 1H), 7.91 – 7.83 (m, 2H), 7.67 (dt, *J* = 7.2, 0.9 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.50 – 7.45 (m, 3H), 7.42 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.37 – 7.33 (m, 1H), 7.33 – 7.28 (m, 2H), 4.82 (d, *J* = 1.6 Hz, 1H), 4.69 (t, *J* = 1.3 Hz, 1H), 1.95 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.19, 152.60, 139.04, 134.68, 134.09, 130.64, 129.36, 129.01, 128.79, 128.51, 127.58, 126.69, 125.98, 125.55, 125.40, 123.90, 102.10, 78.97, 19.40.

HRMS calcd for $C_{21}H_{18}O_3Na$ [M+Na] 341.1154, found 341.1159.



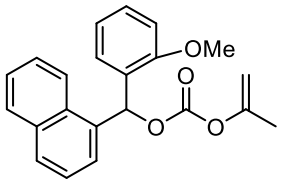
naphthalen-1-yl(p-tolyl)methyl prop-1-en-2-yl carbonate (SM-4-228)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 1H), 7.90 – 7.81 (m, 2H), 7.68 (dt, *J* = 7.2, 0.9 Hz, 1H), 7.51 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.43 (s, 1H), 7.33 – 7.27 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.81 (d, *J* = 1.6 Hz, 1H), 4.68 (p, *J* = 1.2 Hz, 1H), 2.32 (s, 3H), 1.94 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.20, 152.61, 138.38, 136.07, 134.84, 134.06, 130.59, 129.48, 129.22, 128.98, 127.65, 126.64, 125.94, 125.40, 125.23, 123.90, 102.06, 78.91, 21.35, 19.42.

HRMS calcd for $C_{22}H_{24}O_3N$ [M+NH4] 350.1756, found 350.1765.



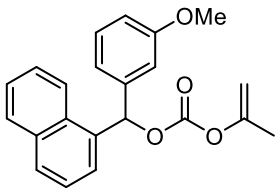
(2-methoxyphenyl)(naphthalen-1-yl)methyl prop-1-en-2-yl carbonate (SM-4-261)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 1H), 7.89 (s, 1H), 7.88 – 7.80 (m, 2H), 7.60 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.34 – 7.27 (m, 1H), 7.22 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.94 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 4.81 (d, *J* = 1.5 Hz, 1H), 4.67 (q, *J* = 1.3 Hz, 1H), 3.87 (s, 3H), 1.95 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.01, 153.22, 152.44, 134.98, 133.91, 130.98, 129.94, 128.98, 128.84, 128.66, 127.19, 126.54, 125.90, 125.39, 124.78, 123.86, 120.75, 110.91, 101.88, 73.10, 55.79, 19.41.

HRMS calcd for $C_{22}H_{21}O_4$ [M+H] 349.1440, found 349.1436.



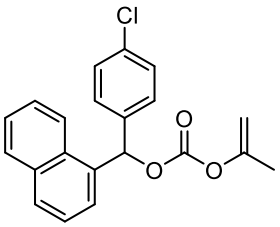
(3-methoxyphenyl)(naphthalen-1-yl)methyl prop-1-en-2-yl carbonate (SM-4-225)

Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dt, *J* = 7.0, 3.6 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.65 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.43 (s, 1H), 7.30 – 7.21 (m, 1H), 7.05 – 6.94 (m, 2H), 6.84 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.82 (d, *J* = 1.6 Hz, 1H), 4.70 (q, *J* = 1.2 Hz, 1H), 3.76 (d, *J* = 0.9 Hz, 3H), 1.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.88, 153.18, 152.57, 140.61, 134.57, 134.07, 130.68, 129.85, 129.40, 129.00, 126.72, 125.98, 125.64, 125.38, 123.86, 119.89, 113.68, 113.38, 102.11, 78.77, 55.40, 19.41.

HRMS calcd for $C_{22}H_{19}O_4$ [M-H] 347.1283, found 347.1288.



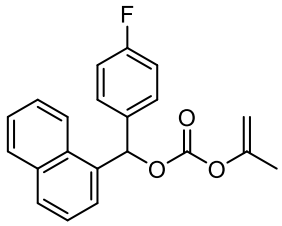
(4-chlorophenyl)(naphthalen-1-yl)methyl prop-1-en-2-yl carbonate (SM-4-226)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 1H), 7.90 – 7.84 (m, 2H), 7.66 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.50 – 7.44 (m, 2H), 7.41 (s, 1H), 7.38 – 7.28 (m, 4H), 4.82 (d, *J* = 1.6 Hz, 1H), 4.70 (dt, *J* = 1.8, 1.1 Hz, 1H), 1.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.13, 152.50, 137.62, 134.44, 134.15, 134.11, 130.44, 129.59, 129.10, 129.01, 129.00, 126.82, 126.09, 125.56, 125.40, 123.73, 102.20, 78.29, 19.38.

HRMS calcd for $C_{21}H_{17}ClO_3Li$ [M+Li] 359.1026, found 359.1016.



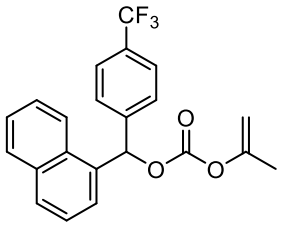
(4-fluorophenyl)(naphthalen-1-yl)methyl prop-1-en-2-yl carbonate (SM-4-273)

Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 1H), 7.90 – 7.84 (m, 2H), 7.68 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.52 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.46 (d, *J* = 4.1 Hz, 1H), 7.43 (s, 1H), 7.39 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.06 – 6.96 (m, 2H), 4.82 (d, *J* = 1.6 Hz, 1H), 4.70 (p, *J* = 1.2 Hz, 1H), 1.95 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.78 (d, *J* = 247.7 Hz), 153.16, 152.53, 134.91 (d, *J* = 3.2 Hz), 134.40, 134.10, 130.43, 129.60 (d, *J* = 8.3 Hz), 129.47, 129.09, 126.76, 126.06, 125.40, 125.25, 123.75, 115.76 (d, *J* = 21.6 Hz), 102.16, 78.32, 19.39.

HRMS calcd for $C_{21}H_{17}FO_3Na$ [M+Na] 359.1059, found 359.1051.



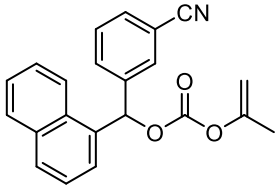
naphthalen-1-yl(4-(trifluoromethyl)phenyl)methyl prop-1-en-2-yl carbonate (SM-5-6)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 1H), 7.93 – 7.85 (m, 2H), 7.66 – 7.57 (m, 3H), 7.55 (s, 3H), 7.47 (s, 3H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.71 (p, *J* = 1.4 Hz, 1H), 1.95 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.13, 152.49, 143.10, 134.17, 133.89, 130.74, 130.48, 130.53, 130.22, 129.83, 129.17, 127.67, 126.97, 126.14 (d, *J* = 12.2 Hz), 125.81 (q, *J* = 3.6 Hz), 125.43, 123.66, 102.25, 78.23, 19.36.

HRMS calcd for $C_{22}H_{18}F_3O_3$ [M+H] 387.1208, found 387.1202.



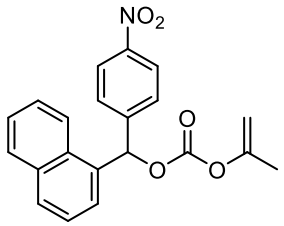
(3-cyanophenyl)(naphthalen-1-yl)methyl prop-1-en-2-yl carbonate (SM-5-58)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 3H), 7.71 (td, *J* = 1.9, 0.7 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.58 (s, 1H), 7.56 – 7.52 (m, 1H), 7.52 – 7.46 (m, 2H), 7.44 (d, *J* = 11.2 Hz, 2H), 4.83 (d, *J* = 1.8 Hz, 1H), 4.71 (dq, *J* = 2.2, 1.2 Hz, 1H), 1.96 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.12, 152.41, 140.92, 134.25, 133.44, 132.13, 131.81, 130.97, 130.38, 130.04, 129.69, 129.28, 127.08, 126.28, 126.05, 125.46, 123.52, 118.64, 113.11, 102.26, 77.88, 19.35.

HRMS calcd for $C_{22}H_{21}N_2O_3$ [M+NH4] 361.1552, found 361.1562.



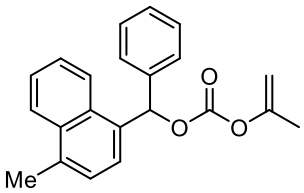
naphthalen-1-yl(4-nitrophenyl)methyl prop-1-en-2-yl carbonate (SM-4-242)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 2H), 7.97 – 7.86 (m, 3H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.61 (s, 2H), 7.54 – 7.51 (m, 1H), 7.51 – 7.44 (m, 3H), 4.83 (d, *J* = 1.8 Hz, 1H), 4.72 (dt, *J* = 2.2, 1.1 Hz, 1H), 1.96 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.09, 152.41, 147.85, 146.34, 134.25, 133.41, 130.44, 130.15, 129.27, 128.06, 127.12, 126.48, 126.30, 125.44, 124.06, 123.56, 102.34, 77.99, 19.34.

HRMS calcd for $C_{21}H_{17}NO_5$ [M+] 363.1107, found 363.1111.



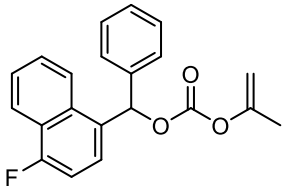
(4-methylnaphthalen-1-yl)(phenyl)methyl prop-1-en-2-yl carbonate (SM-4-268)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.95 (m, 2H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 7.45 – 7.38 (m, 3H), 7.37 – 7.32 (m, 2H), 7.32 – 7.28 (m, 2H), 4.81 (d, *J* = 1.6 Hz, 1H), 4.69 (q, *J* = 1.3 Hz, 1H), 2.71 (s, 3H), 1.94 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.20, 152.62, 139.25, 135.67, 133.21, 132.87, 130.72, 128.75, 128.41, 127.52, 126.32, 126.20, 125.82, 125.50, 125.07, 124.48, 102.06, 79.13, 19.86, 19.42.

HRMS calcd for $C_{22}H_{20}O_3Na$ [M+Na] 355.1310, found 355.1316.



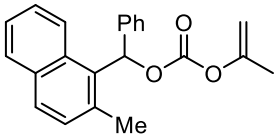
(4-fluoronaphthalen-1-yl)(phenyl)methyl prop-1-en-2-yl carbonate (SM-5-55)

Yellow solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.03 – 7.96 (m, 1H), 7.60 – 7.55 (m, 1H), 7.55 – 7.49 (m, 2H), 7.42 – 7.37 (m, 3H), 7.37 – 7.33 (m, 2H), 7.32 (d, *J* = 7.0 Hz, 1H), 7.16 (dd, *J* = 10.1, 8.0 Hz, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.74 – 4.65 (m, 1H), 1.95 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.26 (d, *J* = 253.6 Hz), 153.16, 152.56, 138.90, 132.09 (d, *J* = 4.5 Hz), 130.67 (d, *J* = 4.5 Hz), 128.84, 128.57, 127.69, 127.40, 126.35 (d, *J* = 1.5 Hz), 125.97 (d, *J* = 9.0 Hz), 124.30 (d, J = 16.3 Hz), 123.97 (d, *J* = 2.5 Hz), 121.49 (d, *J* = 5.7 Hz), 108.90 (d, *J* = 20.1 Hz), 102.14, 78.68, 19.39.

HRMS calcd for $C_{21}H_{17}FO_3Na$ [M+Na] 359.1059, found 359.1066.



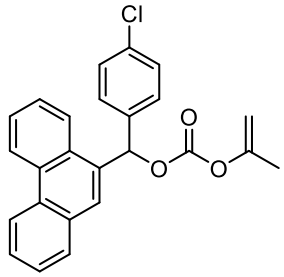
(2-methylnaphthalen-1-yl)(phenyl)methyl prop-1-en-2-yl carbonate (SM-4-277)

Yellow solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.64 (s, 1H), 7.40 – 7.34 (m, 2H), 7.32 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.22 (dt, *J* = 8.3, 1.3 Hz, 2H), 4.78 (d, *J* = 1.5 Hz, 1H), 4.72 – 4.62 (m, 1H), 2.67 (s, 3H), 1.92 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.22, 153.10, 139.32, 136.27, 133.40, 131.66, 131.23, 129.59, 129.43, 128.68, 128.62, 127.69, 126.26, 126.03, 125.89, 124.99, 102.20, 77.27, 20.92, 19.42.

HRMS calcd for $C_{22}H_{20}O_3Li$ [M+Li] 339.1573, found 339.1570.



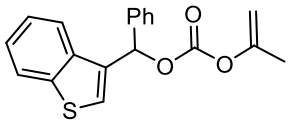
(4-chlorophenyl)(phenanthren-9-yl)methyl prop-1-en-2-yl carbonate (SM-5-42)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 7.99 – 7.87 (m, 3H), 7.73 – 7.67 (m, 1H), 7.64 (dd, *J* = 5.0, 3.2 Hz, 2H), 7.54 (d, *J* = 1.3 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 3H), 7.34 – 7.27 (m, 1H), 7.24 (s, 1H), 4.89 – 4.77 (m, 1H), 4.77 – 4.62 (m, 1H), 1.96 (d, *J* = 10.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.17, 152.53, 137.29, 134.64, 132.30, 131.15, 131.12, 130.77, 129.33, 129.27, 129.17, 129.10, 127.60, 127.20, 127.09, 126.83, 126.80, 124.75, 123.52, 122.73, 102.26, 78.69, 19.40.

HRMS calcd for $C_{25}H_{20}ClO_3$ [M+H] 403.1101, found 403.1100.

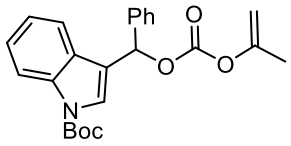


benzo[b]thiophen-3-yl(phenyl)methyl prop-1-en-2-yl carbonate (SM-4-276)

Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 1H), 7.72 – 7.65 (m, 1H), 7.50 – 7.45 (m, 2H), 7.43 (d, *J* = 0.9 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.34 (dd, *J* = 3.4, 1.5 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.10 (s, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.70 (p, *J* = 1.1 Hz, 1H), 1.96 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.16, 152.53, 140.89, 138.08, 137.07, 134.17, 128.86, 128.82, 127.46, 125.70, 124.82, 124.55, 123.05, 122.55, 102.14, 77.07, 19.40.



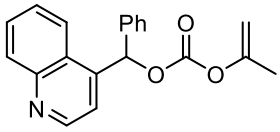
tert-butyl 3-(phenyl(((prop-1-en-2-yloxy)carbonyl)oxy)methyl)-1H-indole-1-carboxylate (SM-4-284)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.57 (s, 1H), 7.53 – 7.46 (m, 2H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 6.6 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.32 – 7.27 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 4.81 (d, *J* = 1.6 Hz, 1H), 4.70 (d, *J* = 1.8 Hz, 1H), 1.95 (s, 3H), 1.66 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.18, 152.60, 149.75, 138.27, 135.94, 128.80, 128.69, 128.39, 127.25, 125.06, 124.91, 123.02, 120.14, 119.35, 115.52, 102.13, 84.29, 75.73, 28.36, 19.42.

HRMS calcd for $C_{24}H_{24}NO_5$ [M-H] 406.1654, found 406.1656.



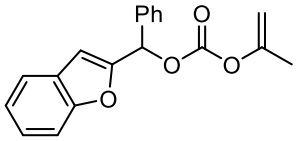
phenyl(quinolin-4-yl)methyl prop-1-en-2-yl carbonate (SM-5-10)

Yellow solid isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 4.5 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.93 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.66 (dd, *J* = 4.5, 0.8 Hz, 1H), 7.50 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.37 – 7.31 (m, 3H), 4.83 (d, *J* = 1.8 Hz, 1H), 4.72 (q, *J* = 1.3 Hz, 1H), 1.96 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.11, 152.33, 150.43, 148.70, 144.17, 137.55, 130.61, 129.55, 129.22, 129.08, 128.02, 127.25, 125.34, 123.68, 118.63, 102.29, 77.60, 19.35.

HRMS calcd for $C_{20}H_{18}NO_3$ [M+H] 320.1287, found 320.1289.



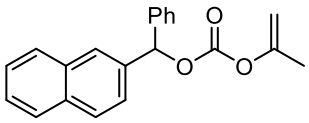
benzofuran-2-yl(phenyl)methyl prop-1-en-2-yl carbonate (SM-4-295)

Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (ddd, *J* = 8.2, 7.2, 1.8 Hz, 3H), 7.49 – 7.44 (m, 1H), 7.41 (dd, *J* = 8.0, 2.0 Hz, 3H), 7.32 – 7.27 (m, 1H), 7.24 – 7.18 (m, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.62 (dt, *J* = 2.0, 1.0 Hz, 1H), 4.84 (d, *J* = 1.8 Hz, 1H), 4.71 (h, *J* = 1.2 Hz, 1H), 1.97 (t, *J* = 1.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.51, 154.14, 153.15, 152.28, 136.24, 129.20, 128.90, 127.79, 127.59, 125.04, 123.16, 121.54, 111.75, 106.66, 102.19, 75.22, 19.37.

HRMS calcd for $C_{19}H_{20}O_4N$ [M+NH4] 326.1392, found 326.1391.



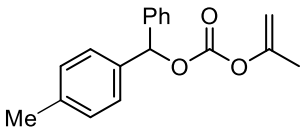
naphthalen-2-yl(phenyl)methyl prop-1-en-2-yl carbonate (4.57)

Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 1.8 Hz, 1H), 7.82 (dd, J = 9.8, 4.7 Hz, 3H), 7.53 – 7.46 (m, 2H), 7.44 (dt, J = 8.1, 1.6 Hz, 3H), 7.39 – 7.34 (m, 2H), 7.32 (d, J = 7.2 Hz, 1H), 6.89 (s, 1H), 4.82 (d, J = 1.7 Hz, 1H), 4.70 (p, J = 1.3 Hz, 1H), 1.96 (d, J = 1.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.17, 152.48, 139.46, 136.88, 133.24, 133.23, 128.81, 128.73, 128.45, 128.38, 127.87, 127.28, 126.57, 126.22, 124.86, 102.16, 81.38, 19.41.

HRMS calcd for $C_{21}H_{18}O_3Na$ [M+Na] 341.1154, found 341.1154.



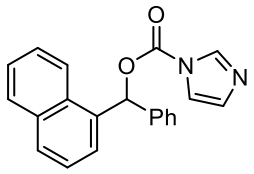
phenyl(p-tolyl)methyl prop-1-en-2-yl carbonate (4.56)

Colorless liquid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 3H), 7.36 – 7.32 (m, 1H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.70 (s, 1H), 4.80 (d, *J* = 1.6 Hz, 1H), 4.68 (p, *J* = 1.2 Hz, 1H), 2.34 (s, 3H), 1.95 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.17, 152.47, 139.77, 138.23, 136.67, 129.46, 128.74, 128.26, 127.20, 127.04, 102.06, 81.22, 21.34, 19.40.

HRMS calcd for $C_{18}H_{18}O_3Na$ [M+Na] 305.1154, found 305.1155.



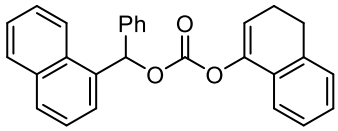
naphthalen-1-yl(phenyl)methyl 1H-imidazole-1-carboxylate (SM-4-299)

Colorless oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (t, *J* = 1.1 Hz, 1H), 8.01 – 7.95 (m, 1H), 7.94 – 7.87 (m, 2H), 7.76 (s, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 1.1 Hz, 1H), 7.49 (tt, *J* = 3.5, 1.8 Hz, 3H), 7.45 – 7.39 (m, 2H), 7.39 – 7.33 (m, 3H), 7.10 – 7.05 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.29, 138.07, 137.36, 134.19, 133.54, 131.02, 130.64, 129.97, 129.21, 129.03, 128.98, 127.58, 127.02, 126.25, 126.05, 125.34, 123.69, 117.40, 79.35.

HRMS calcd for $C_{21}H_{16}N_2O_2$ [M+] 328.1212, found 328.1211.



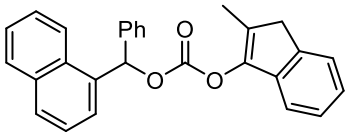
3,4-dihydronaphthalen-1-yl (naphthalen-1-yl(phenyl)methyl) carbonate (4.59)

Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.92 – 7.83 (m, 2H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.40 (m, 6H), 7.39 – 7.28 (m, 3H), 7.19 – 7.11 (m, 2H), 7.11 – 7.01 (m, 2H), 5.79 (s, 1H), 2.92 – 2.76 (m, 2H), 2.52 – 2.29 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.19, 146.37, 138.93, 136.50, 134.61, 134.11, 130.72, 130.21, 129.43, 129.02, 128.79, 128.53, 128.22, 127.70, 127.60, 126.71, 126.64, 126.00, 125.81, 125.38, 123.94, 120.80, 115.43, 79.42, 27.53, 22.11.

HRMS calcd for $C_{28}H_{22}O_3Na$ [M+Na] 429.1467, found 429.1461.



2-methyl-1H-inden-3-yl (naphthalen-1-yl(phenyl)methyl) carbonate (4.60)

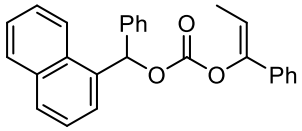
Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 1H), 7.88 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.48 (ddd, *J* = 7.0, 4.5, 1.9 Hz, 4H), 7.40 – 7.35 (m, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.16 – 7.09 (m, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 3.30 (s, 2H), 1.95 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.33, 144.70, 140.14, 139.43, 138.86, 134.58, 134.12, 130.71, 129.47, 129.04, 128.84, 128.63, 128.62, 127.66, 126.74, 126.48, 126.03, 125.60, 125.40, 124.91, 123.89, 117.30, 79.63, 39.14, 12.26.

HRMS calcd for $C_{28}H_{22}O_3Na$ [M+Na] 429.1467, found 429.146534.

Characterization data for (*Z*)-benzyl vinyl carbonates:



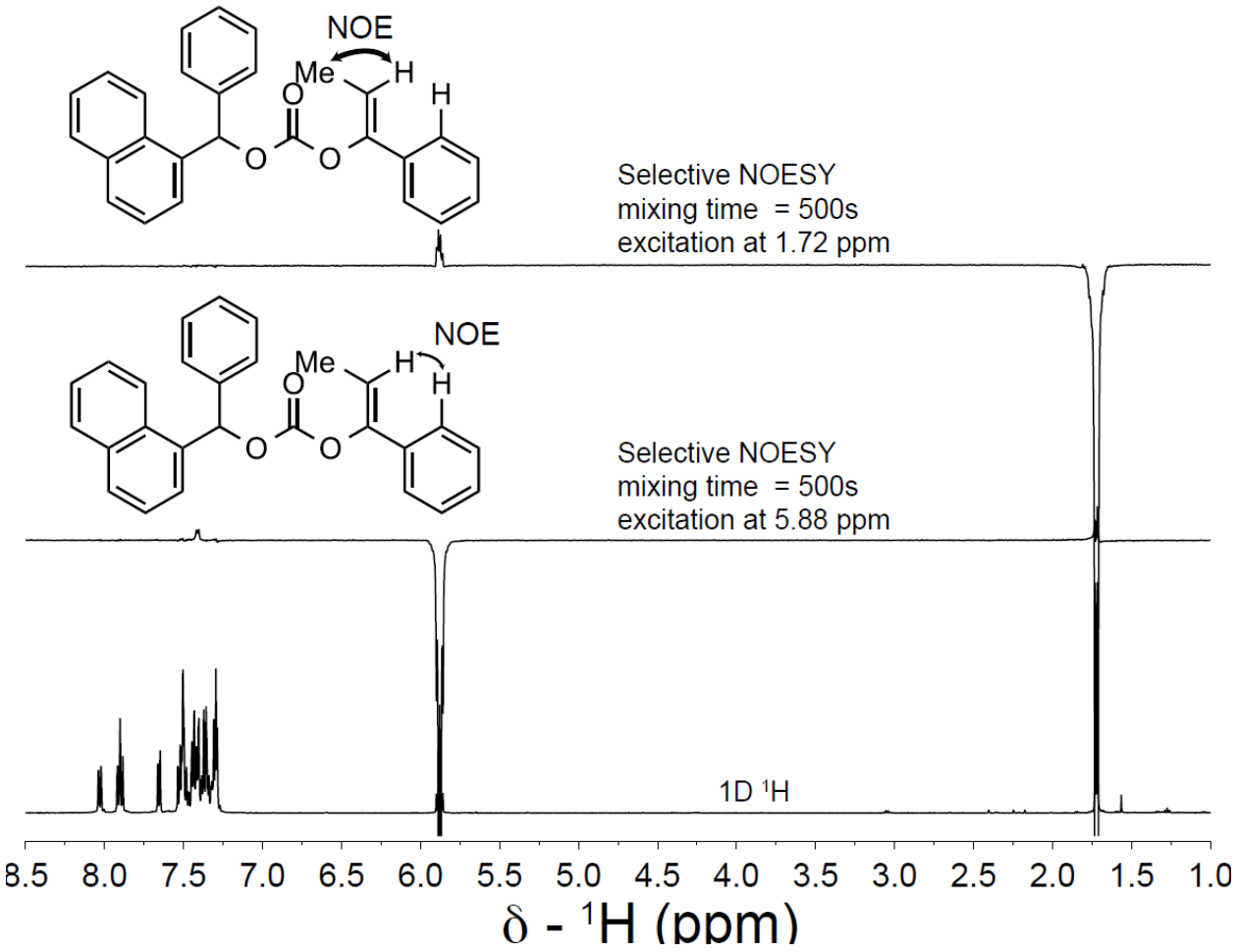
(*Z*)-naphthalen-1-yl(phenyl)methyl (1-phenylprop-1-en-1-yl) carbonate (SM-5-63)

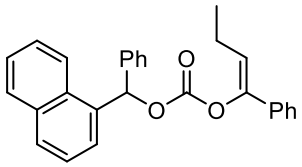
White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.61 (d, *J* = 7.1 Hz, 1H), 7.51 – 7.45 (m, 4H), 7.45 (d, *J* = 1.5 Hz, 1H), 7.40 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.39 – 7.36 (m, 2H), 7.33 (ddd, *J* = 8.7, 7.3, 5.9 Hz, 3H), 7.27 (d, *J* = 6.3 Hz, 2H), 5.90 – 5.78 (m, 1H), 1.69 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.55, 147.68, 138.95, 134.85, 134.68, 134.12, 130.78, 129.41, 129.00, 128.76, 128.69, 128.51, 128.33, 127.55, 126.69, 125.99, 125.72, 125.34, 124.47, 123.92, 113.01, 79.38, 11.40.

HRMS calcd for $C_{27}H_{22}O_3Na$ [M+Na] 417.1467, found 417.1466.





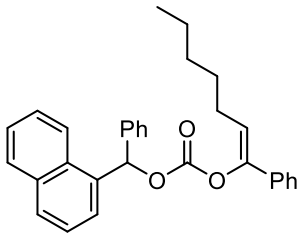
(*Z*)-naphthalen-1-yl(phenyl)methyl (1-phenylbut-1-en-1-yl) carbonate (SM-5-66)

Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.91 – 7.83 (m, 2H), 7.63 – 7.57 (m, 1H), 7.52 – 7.41 (m, 4H), 7.38 (ddd, *J* = 7.7, 4.7, 2.0 Hz, 4H), 7.34 – 7.30 (m, 2H), 7.29 – 7.23 (m, 4H), 5.75 (t, *J* = 7.4 Hz, 1H), 2.12 (p, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.70, 146.38, 138.94, 134.87, 134.66, 134.11, 130.77, 129.39, 128.99, 128.75, 128.68, 128.49, 128.34, 127.55, 126.67, 125.98, 125.73, 125.33, 124.55, 123.94, 120.07, 79.40, 19.49, 13.58.

HRMS calcd for $C_{28}H_{24}O_3Na$ [M+Na] 431.1623, found 431.1619.



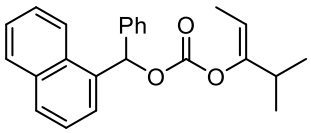
(*Z*)-naphthalen-1-yl(phenyl)methyl (1-phenylhept-1-en-1-yl) carbonate (SM-5-74)

White solid isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.61 (d, *J* = 7.1 Hz, 1H), 7.53 – 7.44 (m, 4H), 7.43 – 7.37 (m, 4H), 7.37 – 7.30 (m, 3H), 7.30 – 7.26 (m, 3H), 5.78 (t, *J* = 7.4 Hz, 1H), 2.09 (q, *J* = 7.5 Hz, 2H), 1.36 (h, *J* = 7.6 Hz, 2H), 1.31 – 1.13 (m, *J* = 3.6 Hz, 4H), 0.86 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.66, 146.67, 138.90, 134.86, 134.62, 134.08, 130.73, 129.38, 128.98, 128.73, 128.67, 128.47, 128.30, 127.53, 126.66, 125.97, 125.73, 125.31, 124.50, 123.91, 118.70, 79.35, 31.63, 28.70, 26.02, 22.56, 14.18.

HRMS calcd for $C_{31}H_{34}O_3N$ [M+NH_4] 468.2539, found 468.2531.



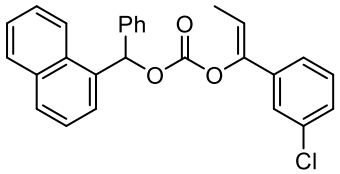
(*Z*)-4-methylpent-2-en-3-yl (naphthalen-1-yl(phenyl)methyl) carbonate (SM-5-79)

Yellow oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 1H), 7.91 – 7.82 (m, 2H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.54 – 7.40 (m, 6H), 7.39 – 7.27 (m, 3H), 5.07 (q, *J* = 6.8 Hz, 1H), 2.43 (hept, *J* = 7.1 Hz, 1H), 1.42 (dd, *J* = 6.9, 1.3 Hz, 3H), 1.02 (dd, *J* = 6.9, 2.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.75, 152.61, 139.13, 134.89, 134.07, 130.76, 129.29, 128.99, 128.75, 128.46, 127.59, 126.65, 125.97, 125.51, 125.35, 123.89, 109.02, 78.80, 32.24, 20.32, 10.63.

HRMS calcd for $C_{24}H_{25}O_3$ [M+H] 361.1804, found 361.1807.



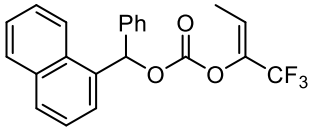
(*Z*)-1-(3-chlorophenyl)prop-1-en-1-yl (naphthalen-1-yl(phenyl)methyl) carbonate (SM-5-85)

Yellow oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 1H), 7.91 – 7.83 (m, 2H), 7.61 (d, *J* = 7.1 Hz, 1H), 7.54 – 7.44 (m, 4H), 7.43 – 7.38 (m, 2H), 7.38 – 7.30 (m, 4H), 7.25 – 7.15 (m, 3H), 5.86 (d, *J* = 7.0 Hz, 1H), 1.69 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.41, 146.37, 138.71, 136.69, 134.78, 134.47, 134.09, 130.71, 129.96, 129.48, 129.03, 128.83, 128.61, 128.36, 127.52, 126.76, 126.04, 125.64, 125.35, 124.63, 123.78, 122.57, 114.56, 79.58, 11.48.

HRMS calcd for $C_{27}H_{21}ClO_3Na$ [M+Na] 451.1077, found 451.1072.



(*Z*)-naphthalen-1-yl(phenyl)methyl (1,1,1-trifluorobut-2-en-2-yl) carbonate (SM-5-86)

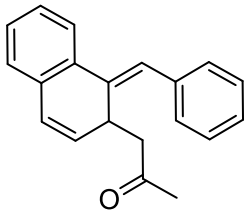
Colorless oil isolated from flash chromatography using: 97:3 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 1H), 7.95 – 7.84 (m, 2H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.54 (s, 2H), 7.52 – 7.48 (m, 2H), 7.48 – 7.43 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 3H), 6.16 (q, *J* = 7.1 Hz, 1H), 1.59 (dd, *J* = 7.1, 2.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.43, 138.32, 136.58 (q, *J* = 36.6 Hz), 134.06 (d, *J* = 4.5 Hz), 130.57, 129.59, 129.07, 128.86, 128.79, 127.58, 126.81, 126.09, 125.39 (d, *J* = 12.4 Hz), 123.67, 121.83 (q, *J* = 3.3 Hz), 120.89, 118.73, 80.41, 77.20, 10.69.

HRMS calcd for $C_{22}H_{17}F_3O_3$ [M+] 386.1130, found 386.1129.

Characterization data for dearomatized ketones:



(*E*)-1-(1-benzylidene-1,2-dihydronaphthalen-2-yl)propan-2-one (4.2)

Yellow oil isolated from flash chromatography using: 96:4 hexanes:EtOAc as eluent.

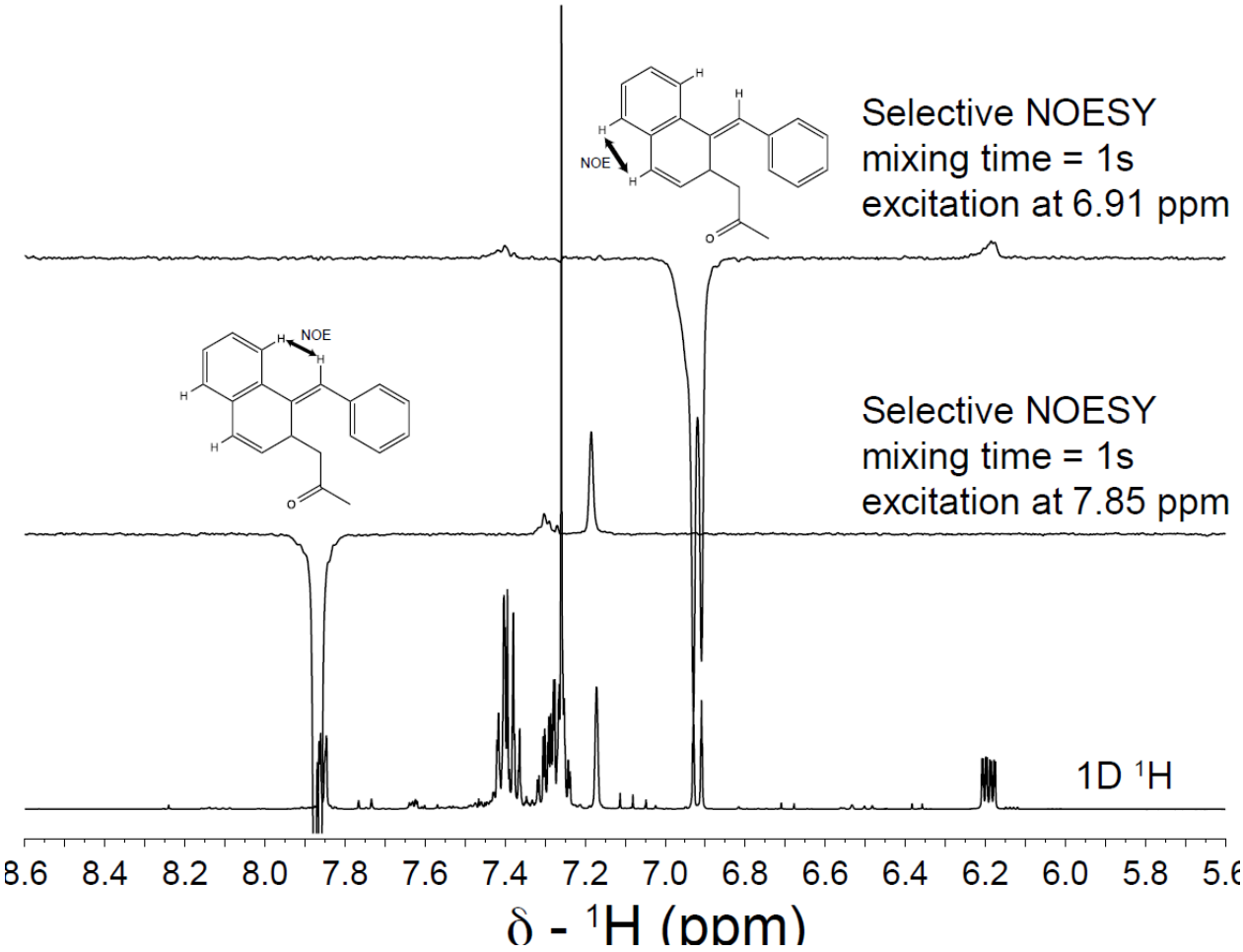
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.82 (m, 1H), 7.44 – 7.39 (m, 3H), 7.38 (s, 1H), 7.33 – 7.27 (m, 3H), 7.24 (d, *J* = 2.7 Hz, 1H), 7.17 (s, 1H), 6.92 (d, *J* = 10.1 Hz, 1H), 6.19 (ddd, *J* = 10.2, 5.0, 1.6 Hz, 1H), 4.14 (dt, *J* = 9.5, 5.0 Hz, 1H), 2.86 (dd, *J* = 17.0, 5.0 Hz, 1H), 2.73 (dd, *J* = 17.1, 8.8 Hz, 1H), 2.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.22, 138.33, 137.63, 133.89, 131.97, 131.04, 129.62, 128.44, 128.34, 127.77, 127.08, 126.86, 125.08, 123.64, 123.17, 53.14, 36.73, 30.82.

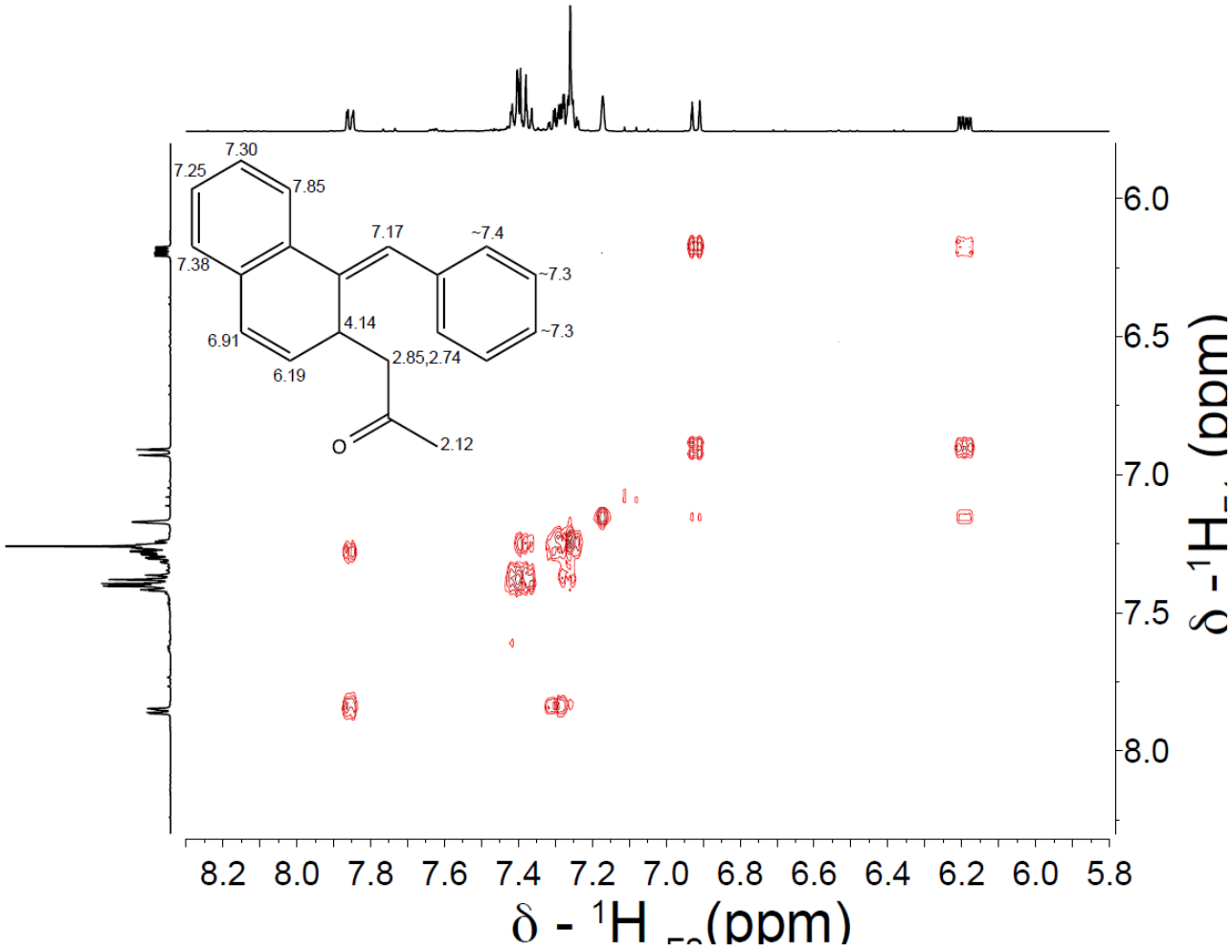
HRMS calcd for $C_{20}H_{18}ONa$ [M+Na] 297.1255, found 297.1255.

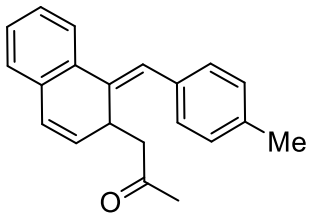
1D selective NOESY and COSY for product **4.2** are provided in the next two pages to support for the (*E*)-configuration of **4.2**.[2]

1D selective NOESY of 4.2



2D COSY of 4.2





(*E*)-1-(1-(4-methylbenzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (4.23)

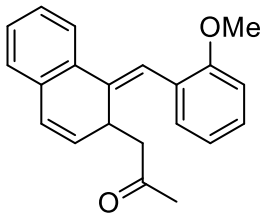
Yellow oil isolated from flash chromatography using: 96:4 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.83 (m, 1H), 7.36 – 7.30 (m, 2H), 7.29 (d, *J* = 4.5 Hz, 1H), 7.28 – 7.27 (m, 1H), 7.24 (d, *J* = 2.6 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.15 (s, 1H), 6.94

(dd, *J* = 10.1, 1.2 Hz, 1H), 6.19 (ddd, *J* = 10.1, 5.0, 1.7 Hz, 1H), 4.14 (dt, *J* = 9.6, 5.0 Hz, 1H), 2.86 (dd, *J* = 17.0, 4.9 Hz, 1H), 2.74 (dd, *J* = 17.0, 8.8 Hz, 1H), 2.39 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.32, 138.18, 136.89, 134.64, 133.99, 131.57, 130.44, 129.50, 129.13, 128.29, 127.60, 126.78, 125.15, 123.64, 123.06, 53.14, 36.68, 30.80, 21.41.

HRMS calcd for $C_{21}H_{20}ONa$ [M+Na] 311.1412, found 311.1418.



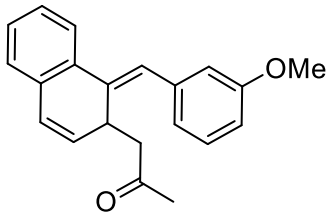
(*E*)-1-(1-(2-methoxybenzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (4.24)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.38 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.26 (s, 1H), 7.25 (q, *J* = 1.8 Hz, 1H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.13 (ddd, *J* = 10.2, 4.9, 1.7 Hz, 1H), 4.14 (dt, *J* = 9.6, 5.0 Hz, 1H), 3.87 (s, 3H), 2.86 (dd, *J* = 17.0, 4.9 Hz, 1H), 2.73 (dd, *J* = 17.0, 8.9 Hz, 1H), 2.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.41, 157.78, 138.10, 133.99, 131.22, 131.02, 130.53, 128.65, 128.24, 127.61, 126.76, 126.43, 125.39, 123.46, 120.25, 119.56, 110.63, 55.65, 53.20, 36.65, 30.84.

HRMS calcd for $C_{21}H_{20}O_2Na$ [M+Na] 327.1361, found 327.1360.



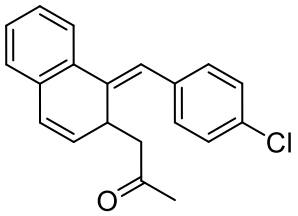
(*E*)-1-(1-(3-methoxybenzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (4.25)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.81 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.26 (d, *J* = 1.1 Hz, 2H), 7.14 (s, 1H), 7.04 – 6.98 (m, 1H), 6.94 (dt, *J* = 9.3, 1.3 Hz, 2H), 6.86 – 6.79 (m, 1H), 6.19 (ddd, *J* = 10.1, 5.0, 1.7 Hz, 1H), 4.14 (dt, *J* = 9.7, 5.1 Hz, 1H), 3.84 (s, 3H), 2.86 (dd, *J* = 17.1, 5.0 Hz, 1H), 2.73 (dd, *J* = 17.2, 8.9 Hz, 1H), 2.12 (s, 3H).

13C NMR (126 MHz, $CDCl_3$) δ 207.26, 159.63, 138.99, 138.34, 133.78, 132.05, 131.24, 129.40, 128.33, 127.79, 126.84, 125.07, 123.42, 123.16, 122.19, 115.16, 112.53, 55.44, 53.10, 36.65, 30.82.

HRMS calcd for $C_{21}H_{20}O_2Na$ [M+Na] 327.1361, found 327.1361.



(*E*)-1-(1-(4-chlorobenzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (4.26)

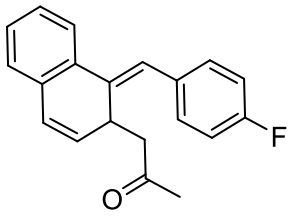
Yellow oil isolated from flash chromatography using: 96:4 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 – 7.72 (m, 1H), 7.26 (s, 3H), 7.24 – 7.20 (m, 2H), 7.18 (s, 2H), 7.03 – 6.98 (m, 1H), 6.77 (dd, *J* = 10.1, 1.0 Hz, 1H), 6.15 (ddd, *J* = 10.2, 5.0, 1.7 Hz, 1H),

4.07 (dt, *J* = 9.8, 5.1 Hz, 1H), 2.79 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.65 (dd, *J* = 17.1, 8.9 Hz, 1H), 2.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.12, 138.34, 136.03, 133.53, 132.75, 132.60, 131.51, 130.83, 128.60, 128.34, 127.94, 126.88, 124.61, 123.11, 122.14, 53.02, 36.64, 30.77.

HRMS calcd for $C_{20}H_{17}ClONa$ [M+Na] 331.0866, found 331.0871.



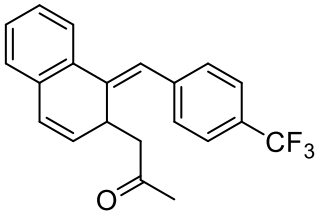
(*E*)-1-(1-(4-fluorobenzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (4.27)

Yellow oil isolated from flash chromatography using: 96:4 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.77 (m, 1H), 7.36 (ddd, *J* = 8.6, 5.6, 2.6 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.24 (d, *J* = 2.9 Hz, 1H), 7.14 – 7.08 (m, 1H), 7.08 – 7.02 (m, 2H), 6.85 (d, *J* = 10.0 Hz, 1H), 6.20 (ddt, *J* = 7.6, 4.3, 2.1 Hz, 1H), 4.14 (dt, *J* = 9.5, 5.0 Hz, 1H), 2.86 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.73 (dd, *J* = 17.1, 8.9 Hz, 1H), 2.12 (d, *J* = 5.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.18, 161.90 (d, *J* = 247.0 Hz), 138.27, 133.67, 133.58 (d, *J* = 3.5 Hz), 132.25, 131.16 (d, *J* = 8.0 Hz), 131.01, 128.34, 127.84, 126.86, 124.71, 123.06, 122.37, 115.39 (d, *J* = 21.3 Hz), 53.08, 36.66, 30.79.

HRMS calcd for $C_{20}H_{17}FOLi$ [M+Li] 299.1423, found 299.1423.



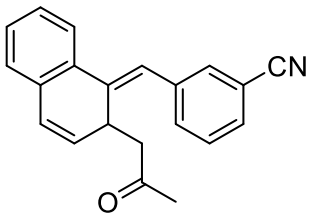
(*E*)-1-(1-(4-(trifluoromethyl)benzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (4.28)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.82 (m, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.31 (dt, *J* = 6.9, 2.3 Hz, 2H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.15 (s, 1H), 6.89 – 6.81 (m, 1H), 6.26 (ddd, *J* = 10.1, 5.0, 1.8 Hz, 1H), 4.16 (dt, *J* = 9.4, 4.9 Hz, 1H), 2.88 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.74 (dd, *J* = 17.1, 8.8 Hz, 1H), 2.13 (d, *J* = 2.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.01, 141.32, 138.54, 133.35, 133.26, 132.63, 129.76, 129.57 (d, *J* = 12.7 Hz), 128.92 (d, *J* = 6.4 Hz), 128.52, 128.31 (d, J = 22.5 Hz), 126.97, 125.34 (q, J = 3.8 Hz), 124.41, 123.24, 121.78, 52.96, 36.63, 30.77.

HRMS calcd for $C_{21}H_{21}F_3ON$ [M+NH4] 360.1575, found 360.1563.



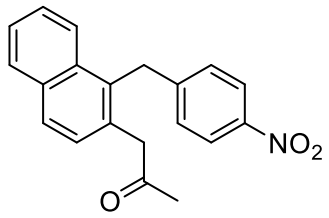
(*E*)-3-((2-(2-oxopropyl)naphthalen-1(2H)-ylidene)methyl)benzonitrile (4.29)

Yellow oil isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.9, 3.4 Hz, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.60 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.52 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.30 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.06 (s, 1H), 6.76 (d, *J* = 10.2 Hz, 1H), 6.27 (ddd, *J* = 10.2, 4.9, 1.7 Hz, 1H), 4.15 (dt, *J* = 10.8, 5.7 Hz, 1H), 2.86 (dd, *J* = 17.3, 4.9 Hz, 1H), 2.72 (dd, *J* = 17.3, 8.8 Hz, 1H), 2.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.81, 138.96, 138.60, 133.95, 133.83, 133.01, 132.96, 132.93, 130.31, 129.27, 128.42, 128.34, 127.00, 123.98, 123.20, 120.62, 119.01, 112.70, 52.87, 36.62, 30.72.

HRMS calcd for $C_{21}H_{17}NONa$ [M+Na] 322.1208, found 322.1205.



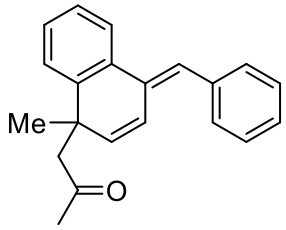
1-(1-(4-nitrobenzyl)naphthalen-2-yl)propan-2-one (4.30)

Yellow solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.96 – 7.83 (m, 2H), 7.57 – 7.41 (m, 2H), 7.39 – 7.26 (m, 4H), 4.53 (s, 2H), 4.14 (s, 2H), 2.16 (s, *J* = 2.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.88, 148.52, 146.71, 134.88, 132.90, 132.37, 131.08, 129.58, 128.14, 127.60, 126.67, 126.54, 124.96, 124.82, 123.96, 49.35, 39.22, 29.33.

HRMS calcd for $C_{20}H_{16}NO_3$ [M-H] 318.1130, found 318.1133.



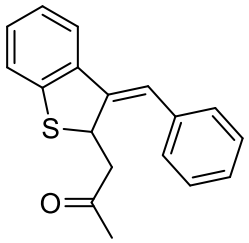
(*E*)-1-(4-benzylidene-1-methyl-1,4-dihydronaphthalen-1-yl)propan-2-one (4.31)

Yellow oil isolated from flash chromatography using: 96:4 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.44 (s, 1H), 7.43 – 7.37 (m, 4H), 7.32 (s, 3H), 7.21 (d, *J* = 1.7 Hz, 1H), 6.91 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.96 (dd, *J* = 10.3, 1.7 Hz, 1H), 3.02 (d, *J* = 14.3 Hz, 1H), 2.72 (d, *J* = 14.4 Hz, 1H), 1.81 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.46, 141.47, 137.60, 136.90, 132.86, 130.61, 129.66, 128.43, 128.04, 127.07, 126.86, 126.53, 123.95, 123.22, 123.11, 57.55, 39.67, 31.34, 30.79.

HRMS calcd for $C_{21}H_{24}ON$ [M+NH4] 306.1858, found 306.1860.



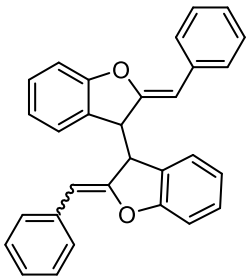
(*E*)-1-(3-benzylidene-2,3-dihydrobenzo[b]thiophen-2-yl)propan-2-one (4.35)

Yellow oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.32 (m, 4H), 7.32 – 7.23 (m, 1H), 7.23 – 7.17 (m, 2H), 7.11 (ddd, *J* = 8.1, 5.0, 3.2 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 5.28 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.01 (dd, *J* = 18.5, 2.9 Hz, 1H), 2.91 (dd, *J* = 18.5, 11.0 Hz, 1H), 2.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.67, 143.42, 142.44, 137.47, 136.27, 129.59, 129.15, 128.47, 127.64, 124.65, 123.03, 122.64, 121.79, 49.97, 44.89, 30.47.

HRMS calcd for $C_{18}H_{16}OSNa$ [M+Na] 303.0820, found 303.0818.

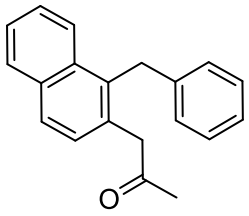


2-((*Z*)-benzylidene)-2'-benzylidene-2,2',3,3'-tetrahydro-3,3'-bibenzofuran (4.38)

Yellow solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.37 (dd, *J* = 8.5, 3.1 Hz, 4H), 7.23 – 7.15 (m, 6H), 7.15 – 7.04 (m, 6H), 6.55 (s, 1H), 6.32 (d, *J* = 1.0 Hz, 1H), 5.03 (s, 1H), 4.99 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.78, 158.00, 154.78, 140.20, 139.54, 128.82, 128.65, 128.59, 128.56, 128.41, 128.29, 127.14, 126.98, 123.61, 123.54, 122.62, 122.55, 120.81, 120.72, 111.15, 111.06, 104.24, 103.48, 50.23, 50.13.



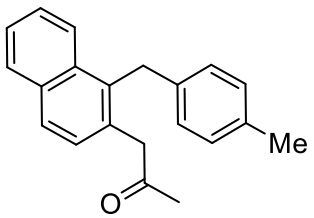
1-(1-benzylnaphthalen-2-yl)propan-2-one (4.3)

White solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.50 (dddd, *J* = 15.1, 8.2, 6.9, 1.5 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.21 (dt, *J* = 9.3, 3.0 Hz, 3H), 4.46 (s, 2H), 4.11 (s, 2H), 2.14 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.29, 140.55, 136.81, 132.72, 132.68, 130.19, 128.93, 128.65, 128.15, 127.21, 126.37, 126.29, 126.16, 125.21, 124.67, 49.50, 39.23, 29.16.

HRMS calcd for $C_{20}H_{18}ONa$ [M+Na] 297.1255, found 297.1258.



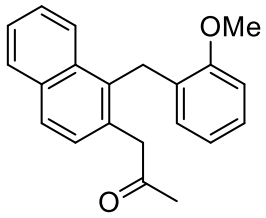
1-(1-(4-methylbenzyl)naphthalen-2-yl)propan-2-one (4.40)

White solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.17 (m, 1H), 8.13 – 7.98 (m, 1H), 7.78 – 7.55 (m, 2H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.45 – 7.34 (m, 1H), 7.26 (s, 4H), 4.57 (s, 2H), 4.26 (s, 2H), 2.48 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.35, 137.45, 137.10, 135.77, 132.71, 132.70, 130.09, 129.34, 128.81, 128.16, 127.11, 126.34, 126.13, 125.22, 124.65, 49.51, 38.80, 29.15, 21.18.

HRMS calcd for $C_{21}H_{21}O$ [M+H] 289.1592, found 289.1581.



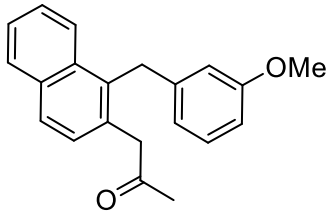
1-(1-(2-methoxybenzyl)naphthalen-2-yl)propan-2-one (4.41)

White solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 1H), 7.90 (dd, *J* = 8.4, 4.5 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.31 (t, *J* = 6.3 Hz, 1H), 7.21 (td, *J* = 8.7, 8.1, 5.7 Hz, 2H), 6.96 – 6.89 (m, 1H), 6.85 (td, *J* = 6.5, 5.5, 1.9 Hz, 1H), 6.83 – 6.75 (m, 1H), 4.42 (d, *J* = 5.1 Hz, 2H), 4.10 (d, *J* = 5.3 Hz, 2H), 3.89 (d, *J* = 5.4 Hz, 3H), 2.12 (s, *J* = 5.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.48, 157.31, 136.81, 132.92, 132.63, 130.25, 129.87, 128.84, 128.23, 127.54, 126.92, 126.30, 126.04, 125.34, 124.60, 120.65, 110.29, 55.56, 49.58, 32.75, 29.17.

HRMS calcd for $C_{21}H_{20}O_2Na$ [M+Na] 327.1361, found 327.1363.



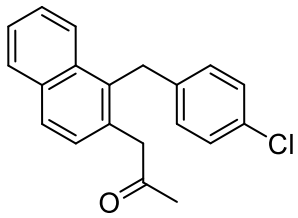
1-(1-(3-methoxybenzyl)naphthalen-2-yl)propan-2-one (4.42)

White solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 1H), 7.94 – 7.86 (m, 1H), 7.55 – 7.44 (m, 2H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.22 – 7.15 (m, 1H), 6.80 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.75 (dd, *J* = 6.8, 1.1 Hz, 2H), 4.42 (s, 2H), 4.10 (s, 2H), 3.75 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.35, 159.90, 142.23, 136.66, 132.74, 130.24, 129.62, 128.16, 127.23, 126.40, 126.20, 125.20, 124.68, 121.42, 114.97, 111.37, 55.30, 49.55, 39.28, 29.18.

HRMS calcd for $C_{21}H_{20}O_2Na$ [M+Na] 327.1361, found 327.1360.



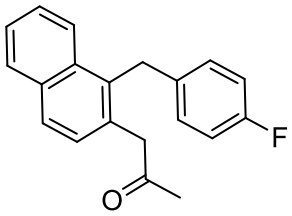
1-(1-(4-chlorobenzyl)naphthalen-2-yl)propan-2-one (4.43)

White solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.34 (d, *J* = 7.1 Hz, 1H), 7.30 – 7.21 (m, 3H), 7.18 – 7.08 (m, 2H), 4.41 (s, 2H), 4.12 (s, 2H), 2.15 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.15, 139.06, 136.21, 132.78, 132.53, 132.07, 130.50, 130.23, 128.77, 128.14, 127.25, 126.48, 126.29, 125.05, 124.78, 49.45, 38.63, 29.23.

HRMS calcd for $C_{20}H_{17}ClOLi$ [M+Li] 315.1128, found 315.1031.



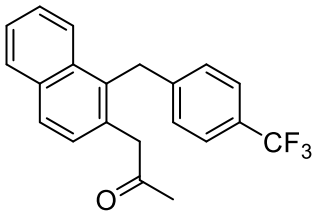
1-(1-(4-fluorobenzyl)naphthalen-2-yl)propan-2-one (4.44)

White solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.6 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.51 (ddd, *J* = 9.5, 7.9, 1.4 Hz, 2H), 7.34 (d, *J* = 7.1 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.16 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 4.12 (s, 2H), 2.15 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.14, 161.54 (d, *J* = 244.2 Hz), 136.59, 136.16 (d, *J* = 3.3 Hz), 132.76, 132.54, 130.38, 130.26 (d, *J* = 7.8 Hz), 128.13, 127.14, 126.43, 126.23, 125.06, 124.75, 115.42 (d, *J* = 21.4 Hz), 49.43, 38.42, 29.20.

HRMS calcd for $C_{20}H_{17}FONa$ [M+Na] 315.1161, found 315.1160.



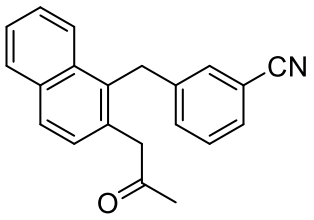
1-(1-(4-(trifluoromethyl)benzyl)naphthalen-2-yl)propan-2-one (4.45)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (ddd, *J* = 17.5, 7.8, 1.4 Hz, 2H), 7.56 – 7.44 (m, 4H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.25 (s, 1H), 4.50 (s, 2H), 4.12 (s, 2H), 2.15 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.05, 144.76, 135.67, 132.84, 132.51, 130.74, 129.16, 128.84, 128.46, 128.16, 127.44, 126.57, 126.42, 125.62 (q, *J* = 3.7 Hz), 124.99, 124.86, 49.46, 39.12, 29.27.

HRMS calcd for $C_{21}H_{17}F_3OLi$ [M+Li] 349.1392, found 349.1394.



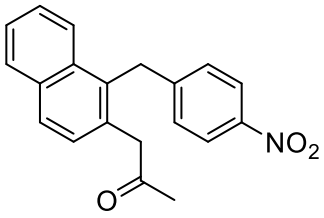
3-((2-(2-oxopropyl)naphthalen-1-yl)methyl)benzonitrile (4.46)

Yellow solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (ddd, *J* = 8.7, 7.6, 1.5 Hz, 2H), 7.56 – 7.49 (m, 2H), 7.49 – 7.46 (m, 2H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.37 (dd, *J* = 7.4, 5.2 Hz, 2H), 7.29 – 7.23 (m, 1H), 4.46 (s, 2H), 4.13 (s, 2H), 2.16 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.92, 142.16, 135.01, 133.32, 132.87, 132.32, 132.27, 130.98, 130.17, 129.44, 128.11, 127.51, 126.61, 126.49, 124.93, 124.78, 119.08, 112.68, 49.37, 38.79, 29.29.

HRMS calcd for $C_{21}H_{17}NO$ [M+] 299.1310, found 299.1314.



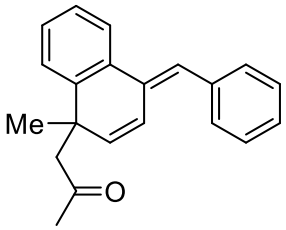
1-(1-(4-nitrobenzyl)naphthalen-2-yl)propan-2-one (4.47)

White solid isolated from flash chromatography using: 95:5 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, CDCl3) δ 8.15 – 8.09 (m, 2H), 7.94 – 7.86 (m, 2H), 7.53 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.47 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.28 (d, *J* = 7.1 Hz, 1H), 4.53 (s, 2H), 4.14 (s, 2H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.88, 148.51, 146.70, 134.88, 132.89, 132.36, 131.08, 129.58, 128.14, 127.60, 126.66, 126.54, 124.96, 124.82, 123.95, 49.35, 39.21, 29.33.

HRMS calcd for $C_{20}H_{21}N_2O_3$ [M+NH4] 337.1552, found 337.1556.



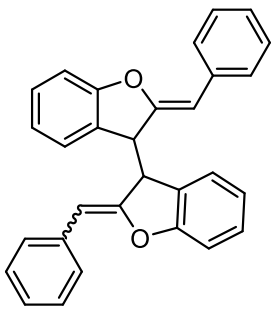
(*E*)-1-(4-benzylidene-1-methyl-1,4-dihydronaphthalen-1-yl)propan-2-one (4.48)

Yellow oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.37 – 7.33 (m, 1H), 7.33 – 7.29 (m, 1H), 7.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.21 (d, *J* = 1.5 Hz, 1H), 6.92 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.96 (dd, *J* = 10.3, 1.7 Hz, 1H), 3.02 (d, *J* = 14.3 Hz, 1H), 2.72 (d, *J* = 14.4 Hz, 1H), 1.81 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.48, 141.46, 137.60, 136.90, 132.85, 130.61, 129.66, 128.43, 128.04, 127.07, 126.86, 126.53, 123.94, 123.22, 123.11, 57.55, 39.67, 31.34, 30.79.

HRMS calcd for $C_{21}H_{24}ON$ [M+NH4] 306.1858, found 306.1848.



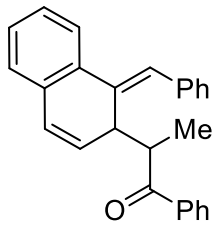
2-((*Z*)-benzylidene)-2'-benzylidene-2,2',3,3'-tetrahydro-3,3'-bibenzofuran (4.55)

Yellow solid isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.40 (dt, *J* = 12.7, 7.3 Hz, 6H), 7.25 (dd, *J* = 7.3, 1.8 Hz, 5H), 7.20 (d, *J* = 8.0 Hz, 4H), 7.19 – 7.16 (m, 4H), 7.16 – 7.13 (m, 3H), 7.14 – 7.08 (m, 3H), 6.59 (d, *J* = 2.0 Hz, 2H), 6.36 (d, *J* = 2.0 Hz, 1H), 5.08 (d, *J* = 2.1 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.78, 158.00, 154.77, 140.20, 139.53, 128.82, 128.65, 128.59, 128.55, 128.40, 128.29, 127.13, 126.97, 123.61, 123.54, 122.62, 122.55, 120.81, 120.71, 111.15, 111.06, 104.24, 103.48, 50.22, 50.12.

HRMS calcd for $C_{30}H_{23}O_2$ [M+H] 415.1698, found 415.1694.



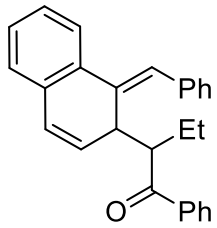
(*E*)-2-(1-benzylidene-1,2-dihydronaphthalen-2-yl)-1-phenylpropan-1-one (4.61)

Yellow oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.92 – 7.83 (m, 3H), 7.78 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.53 – 7.46 (m, 3H), 7.46 – 7.42 (m, 3H), 7.42 – 7.34 (m, 9H), 7.34 – 7.28 (m, 5H), 7.26 (s, 4H), 7.21 (d, *J* = 2.3 Hz, 2H), 7.10 (s, 1H), 7.05 (d, *J* = 10.3 Hz, 1H), 6.84 (d, *J* = 9.9 Hz, 1H), 6.25 (ddd, *J* = 10.0, 5.6, 1.6 Hz, 1H), 6.02 (ddd, *J* = 10.3, 5.2, 1.7 Hz, 1H), 4.14 (d, *J* = 4.9 Hz, 1H), 3.95 (q, *J* = 5.4, 4.5 Hz, 2H), 3.70 – 3.55 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.65, 202.87, 137.59, 137.52, 137.42, 137.17, 136.89, 136.51, 135.62, 135.11, 133.12, 133.09, 131.93, 131.82, 131.37, 129.73, 129.66, 129.57, 128.95, 128.88, 128.74, 128.66, 128.63, 128.60, 128.49, 128.43, 128.28, 127.66, 127.60, 127.12, 126.91, 126.85, 126.84, 126.79, 124.14, 123.79, 123.38, 123.04, 49.37, 48.57, 45.01, 43.12, 15.92, 11.69.

HRMS calcd for $C_{26}H_{22}ONa$ [M+Na] 373.1568, found 373.1571.



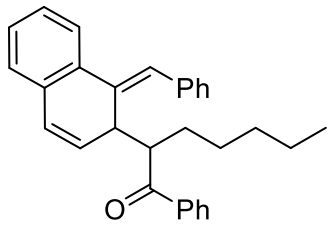
(*E*)-2-(1-benzylidene-1,2-dihydronaphthalen-2-yl)-1-phenylbutan-1-one (4.62)

Colorless oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.86 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.61 – 7.53 (m, 1H), 7.53 – 7.47 (m, 2H), 7.47 – 7.44 (m, 1H), 7.44 – 7.41 (m, 2H), 7.40 – 7.32 (m, 3H), 7.32 – 7.27 (m, 2H), 7.20 (s, 1H), 7.05 – 6.98 (m, 1H), 6.03 (ddd, *J* = 10.2, 5.2, 1.6 Hz, 1H), 4.00 (t, *J* = 5.1 Hz, 1H), 3.79 (ddd, *J* = 10.4, 4.9, 3.3 Hz, 1H), 1.95 (ddd, *J* = 13.8, 10.4, 7.1 Hz, 1H), 1.36 (dd, *J* = 6.2, 3.2 Hz, 1H), 0.73 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.52, 137.97, 137.58, 137.36, 135.14, 133.11, 131.42, 129.75, 129.15, 128.91, 128.44, 128.40, 128.38, 127.60, 127.14, 127.08, 126.84, 123.79, 123.07, 56.49, 43.13, 20.26, 12.61.

HRMS calcd for $C_{27}H_{24}ONa$ [M+Na] 387.1725, found 387.1724.



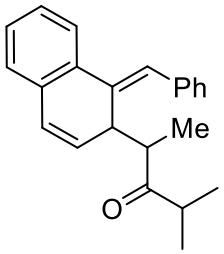
(*E*)-2-(1-benzylidene-1,2-dihydronaphthalen-2-yl)-1-phenylheptan-1-one (4.63)

Yellow oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 2H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.44 – 7.36 (m, 4H), 7.34 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.20 (s, 1H), 7.01 (d, *J* = 10.2 Hz, 1H), 6.05 (ddd, *J* = 10.3, 5.1, 1.6 Hz, 1H), 4.07 – 3.92 (m, 1H), 3.91 – 3.73 (m, 1H), 2.01 – 1.82 (m, 1H), 1.38 – 1.23 (m, 2H), 1.11 (q, *J* = 4.2, 3.6 Hz, 5H), 0.74 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.72, 137.91, 137.64, 137.36, 135.14, 133.09, 131.48, 129.74, 129.30, 128.90, 128.44, 128.40, 128.38, 127.57, 127.13, 127.08, 126.82, 123.78, 123.08, 54.66, 43.21, 32.07, 27.73, 27.23, 22.54, 14.10.

HRMS calcd for $C_{30}H_{30}ONa$ [M+Na] 429.2194, found 429.2191.



(*E*)-2-(1-benzylidene-1,2-dihydronaphthalen-2-yl)-4-methylpentan-3-one (4.64)

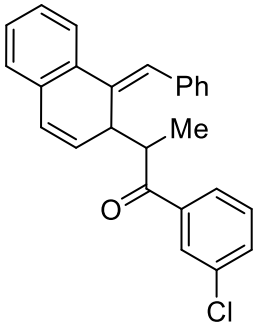
Yellow oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 1H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.29 (dd, *J* = 7.7, 2.1 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.18 (s, 1H), 7.01 (d, *J* = 10.2 Hz, 1H),

6.08 (ddd, *J* = 10.2, 5.4, 1.6 Hz, 1H), 4.00 (t, *J* = 5.4 Hz, 1H), 3.11 – 2.97 (m, 1H), 2.67 (p, *J* = 6.9 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.98 (dd, *J* = 9.8, 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.84, 137.60, 135.04, 131.51, 129.70, 129.66, 128.50, 128.43, 127.47, 127.22, 127.12, 126.77, 123.69, 123.08, 52.89, 42.83, 40.01, 18.70, 18.17, 12.44.

HRMS calcd for $C_{23}H_{24}ONa$ [M+Na] 339.1725, found 339.1729.



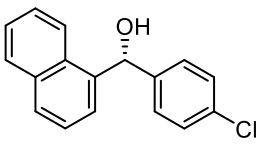
(*E*)-2-(1-benzylidene-1,2-dihydronaphthalen-2-yl)-1-(3-chlorophenyl)propan-1-one (4.65)

Colorless oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.70 (m, 2H), 7.66 (s, 1H), 7.50 – 7.44 (m, 1H), 7.36 (d, *J* = 4.3 Hz, 4H), 7.29 (dd, *J* = 6.1, 2.1 Hz, 4H), 7.22 (d, *J* = 5.1 Hz, 1H), 7.07 (s, 1H), 6.85 (d, *J* = 9.9 Hz, 1H), 6.21 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.92 (t, *J* = 6.2 Hz, 1H), 3.61 (p, *J* = 6.8 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 3H).

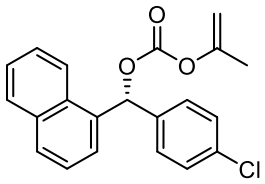
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.37, 138.83, 137.42, 136.34, 135.43, 135.00, 132.91, 131.63, 130.98, 129.90, 129.67, 129.44, 128.72, 128.45, 127.20, 126.97, 126.62, 124.37, 123.33, 49.00, 45.17, 16.01.

HRMS calcd for $C_{26}H_{21}ClONa$ [M+Na] 407.1179, found 407.1177.



(*R*)-(4-chlorophenyl)(naphthalen-1-yl)methanol (*R*-4.68)

HPLC analysis: 75%ee (Chiralcel OD-H, 85:15 Hexanes/isopropanol, 0.55 mL/min, 254 nm, major R_t = 44.0 min, minor R_t = 20.1 min).



(*R*)-(4-chlorophenyl)(naphthalen-1-yl)methyl prop-1-en-2-yl carbonate (*R*-4.69)

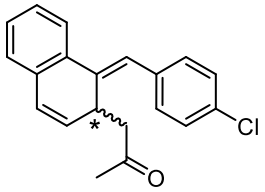
Colorless oil isolated from flash chromatography using: 98:2 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.1 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.43 (m, 3H), 7.41 (s, 1H), 7.32 (q, *J* = 8.4 Hz, 4H), 4.81 (s, 1H), 4.70 (d, *J* = 2.1 Hz, 1H), 1.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.14, 152.51, 137.63, 134.45, 134.16, 134.12, 130.45, 129.59, 129.10, 129.01, 126.83, 126.10, 125.57, 125.40, 123.74, 102.20, 78.30, 19.38.

HRMS calcd for $C_{21}H_{16}ClO_3$ [M-H] 351.0788, found 351.0777.

HPLC analysis: 74%ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 25.8 min, minor R_t = 40.7 min).



(*E*)-1-(1-(4-chlorobenzylidene)-1,2-dihydronaphthalen-2-yl)propan-2-one (*R* or *S* 4.26)

Yellow oil isolated from flash chromatography using: 94:6 hexanes:EtOAc as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.74 (m, 1H), 7.27 (s, 3H), 7.26 – 7.21 (m, 2H), 7.20 (s, 2H), 7.05 – 6.99 (m, 1H), 6.78 (dd, *J* = 10.1, 1.0 Hz, 1H), 6.16 (ddd, *J* = 10.2, 5.0, 1.7 Hz, 1H),

4.08 (dt, *J* = 9.8, 5.1 Hz, 1H), 2.80 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.66 (dd, *J* = 17.1, 8.9 Hz, 1H), 2.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.12, 138.34, 136.03, 133.53, 132.75, 132.60, 131.51, 130.83, 128.60, 128.34, 127.94, 126.88, 124.61, 123.11, 122.14, 53.02, 36.64, 30.77.

HRMS calcd for $C_{20}H_{17}ClONa$ [M+Na] 331.0866, found 331.0873.

HPLC analysis: 65%ee (Chiralpak AD-H, 98:2 Hexanes/isopropanol, 0.5 mL/min, 254 nm, major R_t = 32.9 min, minor R_t = 28.4 min).

References

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2. Peng, B.; Zhang, S.; Yu, X.; Feng, X.; Bao, M. Nucleophilic Dearomatization of Chloromethyl Naphthalene Derivatives via η^3-Benzylpalladium Intermediates: A New Strategy for Catalytic Dearomatization. *Org. Lett.* **2011,** *13* (19), 5402-5405.